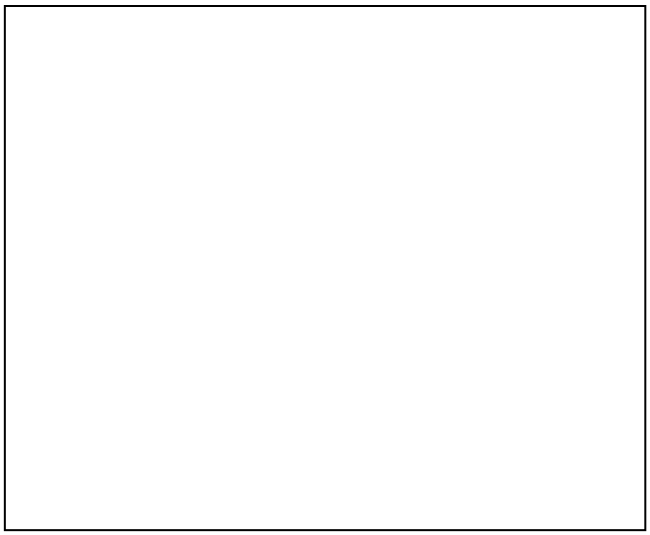
CENTERS FOR DISEASE CONTROL AND PREVENTION

NATIONAL IMMUNIZATION PROGRAM

RECORD OF THE MEETING OF THE

ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

February 26-27, 2003



Atlanta Marriott Century Center Hotel
Atlanta, Georgia

Table of Contents

MINUTES OF THE MEETING

FEBRUARY 26, 2003
- OPENING COMMENTS 1
- INFLUENZA 2
  - Influenza Strain Activity 2
  - Influenza vaccine target groups in the U.S. 5
  - Changes for ACIP 2003 Influenza Vaccine Recommendation 8
  - Future Workgroup Plans. 13
  - Vote 13
- HIV VACCINE 13
  - Phase III Efficacy Trial of AIDSVAX B/B 14
  - HIV Workgroup Response 17
- SMALLPOX 18
  - CDC Smallpox Program 18
  - DOD Smallpox Program 20
  - ACIP Vaccine Safety Monitoring Workgroup 20
  - Civilian Safety Monitoring Activities23
  - Use of VIG in an Inadvertent Vaccination Setting 25
- Pediarix™ PRESENTATION 31
  - ACIP Consideration of Pediarix™ Recommendation 36
  - Programmatic Issues Related to Pediarix™ 41
- VFC RESOLUTIONS 42
  - Vote 45

FEBRUARY 27, 2003
- AGENCY UPDATES45
- EVIDENCE-BASED TABLES IN ACIP RECOMMENDATIONS 50
- IOM IMMUNIZATION SAFETY REVIEW COMMITTEE UPDATE 51
  - Hepatitis B Vaccine and CNS/PNS Neurological Disorders 51
  - SV 40 Contamination of Polio Vaccines 52
- VACCINE STORAGE AND COLD CHAIN ERRORS 54
- SHOTS 2003 PDA SOFTWARE 56
- VACCINE SUPPLY UPDATE 57
- VARICELLA VACCINATION PROGRAM UPDATE 59
- CHANGING EPIDEMIOLOGY OF PNEUMOCOCCAL DISEASE 65
  - Considerations for Resuming the Routine Pneumococcal Schedule 67
- CLOSING COMMENTS 68
- ATTACHMENTS 70
  - Attachment #1: Attendance 71
  - Attachment #2: Tables of VaxGen Vaccine Efficacy Trial Results 76

CENTERS FOR DISEASE CONTROL AND PREVENTION
NATIONAL IMMUNIZATION PROGRAM
ADVISORY COMMITTEE ON IMMUNIZATION PRACTICES

MINUTES OF THE MEETING
February 26-27, 2003

FEBRUARY 26, 2003

A meeting of the Advisory Committee on Immunization Practices (ACIP) was convened by the Centers for Disease Control and Prevention's (CDC) National Immunization Program (NIP) at the Atlanta Marriott Century Center Hotel in Atlanta, Georgia, on February 26-27, 2003. The meeting agenda (posted on CDC's Website, http://www.CDC.gov/nip/) principally addressed the use of smallpox vaccine, but also addressed the influenza vaccine recommendation and the 2003 recommended childhood immunization and catch-up schedules. The meeting was convened by ACIP Chairmen Dr. John Modlin at 8:35 a.m.

Those present are listed in Attachment #1.

OPENING COMMENTS

ACIP Executive Secretary Dr. Dixie Snider made several announcements:

- Dr. Robert Belshe had submitted his resignation for personal and professional reasons.
- The ACIP home page is: www.CDC.gov/nip/acip.
- The remaining 2003 ACIP meetings will be held June 18-19 and October 15-16.
- He requested that the members be attentive to maintaining a quorum for this meeting. If a quorum of eight members is not eligible to vote on a motion due to conflicts of interest, the Executive Secretary is deputized to appoint the liaisons as voting members. He announced that public comment is enabled at ACIP meetings by random selection of the names of those who sign up to speak.
- He welcomed Dr. Robert Scalettar, representing the American Association of Health Plans; Dr. Julie McMillan, present for Dr. Jon Abramson of the AAP; and Ms. Dee Gardner, of the CDC Office of Committee Management, who will manage the committee until Ms. Gloria Kovach is replaced.

Conflict of Interest Statements. Dr. Modlin called for any conflict of interest statements from the members. Members with a conflict may participate in all meeting discussions, but they may not vote on any topic related to that conflict, nor may they introduce or second a vote on the Vaccine for Children (VFC) program. Members declaring potential conflicts of interest were:

- Dr. Myron Levin conducts research with Merck and with SmithKline Beecham (SKB).
- Dr. Paul Offit is co-holder of a patent on a bovine-reassortant rotavirus vaccine and consults on its development with Merck.
- Dr. Rennels is conducting a vaccine trial with Wyeth and is on the Safety Monitoring Board for Aventis Pasteur.
- Dr. Word stated a conflict of interest with MedImmune.
- Dr. Modlin had no conflict, but Chairs the DSMB for Merck's HBV vaccine trial.

Commendation: Dr. Modlin read a letter of appreciation that he had written to Ms. Kovach on behalf of the committee. He thanked her for her unflagging support to the committee despite the many challenges posed to a committee specialist. He commended her as a model of grace and professionalism and as a true public servant in the best sense of the word.

INFLUENZA
Dr. Bonnie Word, Chair of the Influenza Workgroup, introduced the presentations.

Influenza Strain Activity Ms. Lynette Brammer, of NCID, outlined the influenza activity of 2002-03. The data were collected by the World Health Organization (WHO) and the collaborating laboratories of the National Respiratory and Enteric Virus Surveillance System (NREVSS).

U.S. Activity. Influenza B has predominated this season, but a significant amount of type A has also been seen. Of those subtyped, A (H1N1) as well as some A (H3N2) have been identified. The predominating virus has differed regionally: influenza B in the south and midwest; and influenza A in the west and northeast. New England was split about evenly, but now has type A predominating, as does the southeast.

Data come from 750 sentinel provider physicians reporting patients with influenza-like illness ILI). Nationally, only 5 weeks of reporting have been above baseline so far this year and mortality data from the 122 Cities Mortality Reporting System showed that deaths have not reached the epidemic threshold.

Although the season has been mild, children seem to have been disproportionately affected. School outbreaks have closed some schools, mostly due to influenza A, but some due to type B. There have been reports of clusters of influenza-related deaths/severe illness among children. Michigan reported three influenza-related deaths from A (H1N1), one from an as-yet uncharacterized virus, and eight severe influenza-associated illnesses, five with neurologic complications. Of those, 2 were type A (H3N2), and one was A (H1N1). All the H1N1 virus hemagglutinin characterized was similar to the vaccine's New Caledonia strain. There were five unexplained deaths in children ages 2-7 years in Virginia; two of whom were confirmed with influenza B infection. Ms. Brammer noted that the deaths have not been due to a single virus.

Antigenic characterization Most of the influenza B this year is of the type B/Victoria lineage, but some is similar to the type B Hong Kong/330/2001. The type A (H1N1) and A (H1N2) viruses also seen are well matched to the vaccine strain. The few A (H3N2) viruses are mostly similar to the current vaccine strain, but recent virus reactions are being seen to reduced titers of the A Panama strain.

Worldwide Activity. In Europe, type B has predominated, but type A is increasing, mostly of the A (H3N2) subtype. In Asia (Hong Kong and Japan), type A (H3N2) and B viruses are circulating; A (H1N1) has been rare.

This month, two cases of influenza A (H5N1) were confirmed in a single family in Hong Kong, the first human cases since the 1997 Hong Kong outbreak. The index case was in a 9-year old boy who was hospitalized and released; the second case was his 33 year-old father, who died.

The family had recently traveled to Fujian province in southern China. Other respiratory illness occurred in other family members, including an 8-year old sister who died while in China. Hong Kong has intensified its influenza surveillance and CDC is closely monitoring this situation.

Vaccine Strain Selection. The vaccine strain selection for 2003-04 was discussed by the WHO and FDA's Vaccine and Related Biological Products Advisory Committee. In February, VRBPAC agreed to retain the A/New Caledonia/20/99-like (H1N1) components for the next season's vaccine. They deferred the A (H3N2) decision until March so that CDC could assess the new low reactor viruses in case there is a better strain candidate for vaccine production.

Discussion included question if any progress had been made since the last epidemic in developing a seed virus for the H5N1 strain. Dr. Nancy Cox reported much done since 1997 to develop seed viruses appropriate for vaccine production. Currently, the viruses circulating in Hong Kong are antigenically distinct from those in 1997, so the vaccine process is back to square one. But there is a lot of international activity on the issues relevant to developing those seed strains, including intellectual property issues associated with any vaccine virus created with reverse genetics.

Update on influenza-like attributable deaths in the U.S.

Dr. William Thompson, of the NIP's Immunization Safety Branch, described an advance in the modeling of excess influenza deaths. Several models have been used to date: baseline forecasting (Simonsen et al, 1997), the rate difference model (Izurieta et al, 2000), and the new retrospective model.

Modeling. The baseline forecasting models is traditionally used at CDC and does not require viral circulation data. It can fit with other models such as the cyclical regression and ARIMA models. The retrospective and rate difference models require viral data. Both underlying pneumonia and influenza (P&I) and all-cause events can be modeled for death analyses.

The *rate difference model* is based on the definition of the influenza season in winter (identified by sharp reporting peaks at its beginning and end) and the peri-influenza season rates for the balance of the year. In this model, the peri-season rates are subtracted from those of the influenza season rates. The *baseline forecasting model* takes data on the season's time components and adjusts by seasonal trends to project a baseline forward. Any deaths in the subsequent season exceeding that baseline are considered excess influenza deaths.

In the new *retrospective model*, respiratory trends are added to the secular and seasonal trends in the analysis. It includes H3N2, H1N1, and now, estimates for respiratory syncytial virus (RSV). Three different outcomes are modeled: underlying pneumonia death; underlying respiratory and circulatory (R&C) deaths, both drawn from ICD-9 codes; and all cause deaths, drawn from death certificates. An analysis was done of the periods from 1976-99, using death data from the National Center for Health Statistics (NCHS) and the WHO weekly influenza isolate analysis data; and from 1990-99, those data plus RSV isolate data from the NREVSS. For 1990-99, Dr. Thompson delineated the rates for those aged <1 year, 1-4 years, 5-49 years, 50-64 years, and aged 65+. The data reflected the highest rates in the elderly, while rates sharply dropped for those aged 50-64 and younger.

From 1990-99 there were ~ 8,000 annual underlying P&I deaths, mostly among the elderly, 36,000 R&C deaths, and 51,000 all cause deaths. Since the latter was substantially larger than previous estimates, another analysis compared the three different models (baseline, rate difference and retrospective) of the data from 1976-98 for P&I deaths. All the models showed increases over time and a greater number of deaths in the 1990s, supporting that the increases were not model dependent. All correlated for underlying P&I and all-cause deaths. One contribution to rising deaths is the age-specific growth in the U.S. population, particularly in those aged >85. The advantage of the new retrospective model is its specificity by age, influenza type, and sub-type estimates missing from the previous models.

Discussion with Dr. Thompson included:

- *Have you looked at regional differences in the patterns of RSV/influenza overlap?* Yes. The new model can now break it down to the regional level. But one apparent weakness is an insufficient amount of local viral surveillance data in specific locations to fit many of these models.
- *Can this model look at the impact of vaccination such as number of doses administered per year and the deaths averted?* Yes, an averted death model can be fitted to it; those issues are being addressed now. Among the challenges to date is the apparent contradiction of increased vaccination coverage alongside rising deaths. But any studies looking at personal vaccination and mortality and morbidity, show vaccination's benefit. While the rates are relatively constant over this time period, age-adjustment does not work as well when most of the deaths come from those aged >85, a population that has doubled.

Live attenuated influenza vaccine (LAIV).

Dr. Midthun reported VRBPAC's the review of MedImmune's license application for FluMist, first presented in July 2001. The December meeting addressed outstanding issues and ongoing studies along with the safety/efficacy data. This is an intranasally-administered, live influenza virus vaccine with three cold-adapted, temperature sensitive influenza viruses (2 type A, 1 type B). The indication sought was influenza prevention in healthy persons aged 5-64 years in three age groups: 5-17, 18-49 and 50-64 years. This was a change from the original indication, which began at one year. New data from Kaiser safety study in children aged 1-17 years were presented, which suggested an increased risk of asthma in those aged <5 years. New data on shedding of vaccine virus among children in day care was also presented.

The majority of the committee agreed that safety was demonstrated for all three age groups, as was efficacy/effectiveness for those aged 5-49 years. Post-marketing studies suggested to MedImmune included those on annual revaccination; shedding, transmission and genetic stability; tolerance among those at high risk of potential influenza complications; asthma/wheezing risk in children; and safety/efficacy compared to the inactivated vaccine, especially in those aged ≥50 years. Also discussed was monitoring of effectiveness, possibly through surveillance or case-control studies. The FDA's review is ongoing.

Discussion with Dr. Midthun included:

- *Was the risk of reactive airway disease the reason to raise the age from 1-2 to 5 years old?* There was a 3.6-fold relative risk in those individuals aged 18-35 months compared to the placebo cohort for asthma and reactive airway disease (RAD) type condition, mostly seen after the first dose. There were a few with asthma history in that study, although it was

supposed to exclude them, but RAD incidence was seen in both children with- and without asthma history.

- *One advantage of the LAIV is that you can prime the system mucosally, as opposed to parenterally, an ability that is lost as the child gets older. Children with asthma may have a wheezing episode caused by vaccine, but less likely over the next few years to have severe disease when exposed to wild-type virus. The vaccine may show more benefit over a period of years.* That risk-benefit ratio will be addressed further with additional information.

- *Why were there little data on efficacy in those aged 50-64?* The adult effectiveness study (not efficacy) showed the impact on acute febrile illness and then on CDC-like influenza illness in a number of endpoints. It showed overall effectiveness in the entire study population, but it was designed before the ACIP recommended routine influenza vaccination for those aged 50-64. Due to that, FDA requested an adult effectiveness study for that group as well. MedImmune recalled ~600 individuals aged 50-64 to do so. The effectiveness endpoint in that cohort showed no impact on disease endpoints, although there was some amelioration of severity of disease. However, that study had small numbers and it was not powered to look at efficacy.

- Dr. Paradiso hoped that the Wyeth and MedImmune FluMist partners will be able to complete their license application before the next influenza season. MedImmune is manufacturing in anticipation of that. Since the influenza statement will come out in April, the timing will not work to issue an ACIP statement about FluMist product after it is licensed. He hoped for guidance before the season on this vaccine's use, since its age indication differs from the inactivated vaccine. To help that process along, they provided a draft package insert with all the safety/effectiveness data and exclusion criteria. With this, VRBPAC could begin to review the data and hopefully craft a statement before the next season.

- Several thousand children overall were tested for safety, as were several thousand in the 17-50 year-old cohort, but few in those aged 50-64 years. There were no data on the elderly group in the license applications. Dr. Midthun did not have those data but offered to provide them later.

- Dr. Word noted that the ACIP cannot comment in its current recommendations, since the vaccine was not yet licensed. However, there are plans to send out a supplemental recommendation this summer on FluMist, which will probably be on the June ACIP agenda.

- The Kaiser study's informed consent excluded those with asthma, but found upon medical records review that many had had hyperactive airway disease. The ACIP recommendation should consider that parents often do not accurately recall RAD.

Influenza vaccine target groups in the U.S.

Mr. Dennis O'Mara, of the NIP, outlined the U.S. population at increased risk of influenza:

- 83 million with risk factors (36 million aged >64 years; 13 million aged 50-64 years; 18 million aged 19-49 years; 8 million aged 6 months to 18 years (11%), plus 2 million infants who will age into the target group (>6 months) by March 2003; 2 million pregnant women, and 5.5 million other children aged 6-23 months.
- 102 million other target groups (7 million health care workers, and vulnerable household contacts: 10 million aged 50-64, 38 million aged 19-49, 28 million aged 2-18 years) and 19.5 million aged 50-64.
- The total targeted population is 186 million aged >5 months.

The cumulative monthly influenza vaccine distribution, determined from manufacturer-supplied data, showed no shortages in 2002, and the projections for 2003 are higher still. Aventis Pasteur projects production exceeding the 45 million doses produced in 2002, and Evans Vaccines will produce over 35 million doses, up from their 27 million in 2002. Wyeth withdrew from the market after producing 20 million doses in 2002. The question is whether Aventis Pasteur and Evans can make up the difference.

Actual 2002 coverage was calculated from vaccine stock. This includes 12 million doses left unsold from the 95 million produced in 2002 and an estimated ~ 4 million in distributors' hands. With end user wastage (not administered for any reason, breakage, cold chain break, etc.) reducing this further at an estimated 10% (lower end acceptable), about 71 million doses were actually administered in 2002; with 5% wastage (excellent performance), about 75 million doses were actually delivered, not the coverage desired. Preliminary NHIS data indicate declining coverage across all age groups in 2000. That rebounded in 2001, although data are still lacking on the two high risk groups (18-49 and 50-64).

The implications of Wyeth's departure from the U.S. market include a lowered reserve/surge capacity to meet short- and long-term increases in demand or contingencies; that neither remaining producer is a U.S.-owned company, posing implications to supply in emergency situations; and that no other producers presently committed to the U.S. market. That would take 3-5 years to change.

Discussion with Mr. O'Mara included:

- *What are the plans to achieve 2010 coverage goals?* Marketing is needed, and has been done by NIP in the past and will be done this year. NIP also convened the National Influenza Vaccine Immunization Summit with partners from ~60 organizations to address the issues and enhance attention to influenza vaccination, to try to increase the uptake. One important issue is to take full advantage of the participating organizations' communication capacity, including with the general public. Among the workgroups created by this summit was a Communications Workgroup, co-chaired by Dr. Snow of the ACP. NIP hopes to have a consumer representative as the other co-chair. But a continuing problem is the limited public sector funding to carry out adult immunization programs. Dr. Orenstein added that NIP is working, through CMS/Medicare's access, to encourage standing orders in nursing homes, etc. CMS has also increased (almost doubled) the reimbursement for the influenza vaccine, and has big communication campaigns planned to encourage vaccination among the elderly.

- *What percentage of vaccine will be thimerosal-reduced, an important issue to those aged 6-23 months and to pregnant women?* Mr. Hosbach, of Aventis Pasteur, stated that Powderject also has a vaccine suitable for those groups. Aventis Pasteur is waiting to determine the market demand before producing preservative-free vaccine. Last year, of the 1 million doses produced, only 17,000 were sold, since it was introduced late in the season. They are taking great care with the forecast.

  NIP will continue to emphasize vaccination in the optimum October/November period as well as continued vaccination beyond then for those at high risk. They will build on such initiatives as last year's "Catch-up Fortnight" held in December and sponsored by the AMA which had good media pickup despite competition for media attention with smallpox.

- *Do any data indicate major changes in the vaccine delivery site, such as at non-traditional sites, and are those possibilities being explored?* Relevant data are several years old. Workplace vaccination was the number two most common vaccination site in the U.S. after private physicians' offices. Dr. Jim Singleton, of the NIP, reported that this was asked on the Behavioral Risk Factor Surveillance System (BRFSS) in 1999; those data will be compare to the 2002 survey data.

Other comments included:

- There may be difficulty in achieving the 90% rate desired. Surveys indicate that a ceiling apparently exists in vaccination of the elderly, driven by a small percentage who are adamantly opposed to it, although some can be persuaded by their physician.

- The non-use of 20-25 million doses and flat rates are discouraging, but perhaps not mysterious, as the strategy conveys restrictive access to the vaccine despite permissive recommendations. ACIP should consider whether this approach can achieve a 90% immunization rate among those at high risk. Age-based recommendations are more successful than risk condition rates, and it could be that universal recommendations would be even more successful.

- Mr. Kim Bush, of Baxter International, stated that Baxter will begin Phase III clinical trials for a new cell-culture based vaccine this year. It should be licensed in Europe next year and in the U.S. in 2005. But since capacity will be driven by uptake, it is critical for industry to work with the government to help drive that process.

- Dr. Steve Wright, of Maxim Health Care Immunization Community Providers, commented that, since last year's ACIP recommendation on the two-tier approach was issued in February before the vaccine supply situation was determined. Maxim limited their programs in retail/grocery stores, etc. due to the shortage in the previous two years. He felt that the two-tier approach risks limiting the amount of vaccine available for those at high-risk. The Summit discussed establishment of a vaccine alert system. In the absence of a shortage, there should be no two-tier approach. And, since immunization rates drop after Thanksgiving, trying to immunize everyone not at high risk between November 1 and Thanksgiving is too short a period to be successful.

- Dr. Jim Turner, of the American College Health Association, pointed out that college students are a highly mobile group that live, study, and work in the congregate, and move in mass migrations at specific times of the year across the country and/or the world. They are likely to expose multiple people, including those at-risk. He supported a universal recommendation to prevent disease among those at high risk. He also reported anecdotally that his institution achieved 25-30% vaccination rates, with decreased vaccine preventable diseases reported not only among the students but also the community. That herd effect is also indicated by Japanese data.

- Mr. Hosbach pointed out that Aventis Pasteur has an influenza vaccine manufacturing facility in the U.S. as well as in France. And, regarding communication and raising immunization rates, he noted that due to manufacturers' difficulty of leading in promoting vaccination, they find other parties to do that for them (e.g., the National Foundation for Infectious Disease [NFID]) and will be sure that the coordination with CDC is heightened.

Changes for ACIP 2003 Influenza Vaccine Recommendation

Dr. Scott Harper, with the NCID Influenza Branch, reported the primary changes and updates to the 2003 influenza recommendation. References were added (now totaling 320), as was additional clinical information regarding influenza complications in children (page 9) and an update of mortality estimates (page 10).

Other major changes included:
Page 11-12: Additional information is provided on the metabolism of thimerosal and the availability of a reduced thimerosal content vaccine (0.25 ml dose for children aged 6-35 months and 0.5 ml dose for children ≥3 years). The Influenza Workgroup did not suggest expressing a preference for thimerosal-free vaccine due to a limited number of producers and concern about for what age group the thimerosal-free vaccine should be recommended.

Discussion

- The ACIP has not expressed such a preference previously.
- ACOG has worked to improve uptake, developed an education continuum to introduce the concept of vaccinating pregnant women and then to educate them that their babies need it. However, obstetricians as a rule have not endorsed this. The absence of a thimerosal-free vaccine has not been a barrier. Both Aventis Pasteur and Evans make both formulations; one with thimerosal and the other with a trace (<1 microgram/dose), and they are in need of guidance of how much to produce.

- New text (pp 11-12) on the Pichichero study on blood mercury does not tell not the whole story and will confuse the public. Refer to it, but do not include specific language. Public acceptance is more likely of a thimerosal-free product and manufacturers need guidance on how much to manufacturer. However, there is little science to support the need for a thimerosal-free vaccine for infants >6 month old.
  ACIP Response: Since the ACIP has no control over distribution and cannot guarantee delivery, there was no interest in expressing a preference. It also was agreed to delete the added Pichichero paragraph.

1. *Vaccination coverage levels* were updated and were virtually unchanged from 2000-01 estimates: 67% for those aged ≥65 and ~35% for age 50-64 year-olds. An additional paragraph about reducing racial disparities in influenza vaccination rates was inserted. *ACIP Response.* No objection.

2. *Vaccination of those aged 6-23 months*: On page 21, a wording change was suggested to reflect the discussion at the October 2002 ACIP meeting, such that vaccination continues to be encouraged and could be fully recommended within 1 years; and activities for the interim include identifying strategies for efficient vaccination of this age group and reviewing data from ongoing studies on pediatric vaccinations (e.g., VSD date). Updated VAERS data indicate no adverse effects in this age group to date. Presentation of the VSD to ACIP is hoped to be this October. Dr. Harper read the most recent paragraph related to this issue, which was not in the meeting books:

   "Because the children aged 6-23 months are at substantially increased risk for influenza-related hospitalizations, ACIP, the American Academy of Pediatricians, and the American Academy of Family Physicians, continue to encourage vaccination of all children in this age group when feasible. However, the benefits of a full recommendation to vaccinate all children aged 6-23 months will depend on the identification and implementation of practical and efficient influenza vaccination strategies for providers of health care to children. In the interim, identification of potential strategies for influenza vaccination of children, review of additional data from ongoing studies among the 6-23 month old influenza vaccine recipients, and efforts to educate parents and provider about the impact of influenza and the potential benefits and risks of vaccinating young children will continue. The full recommendation could be made within the next year."

Discussion

- AAP is anxious to be concurrent with ACIP recommendations, but wants to move to a full recommendation. The longer there is an "encouragement" instead, children will not receive two doses of trivalent. There are no data on pediatrician readiness to comply, but such practical things will not even be addressed until there is a full recommendation. New strategies are needed for this vaccination because it will be difficult to implement: it is annual, unlike most; and it requires two doses at first immunization. Delivery strategies that are practitioner-friendly, or even delivered outside the practitioner's office, are needed

- Implementation studies are underway, but much education is still needed, and committees other than ACIP still require discussion.

- VSD data could be presented at the next meeting, something the Influenza Workgroup asked for. But the comment that strategies need to be identified to smooth implementation is recurrent. The AAP and AAFP would like to provide members with some information, such as current implemented and effective practices, to prompt initial thinking about whether these methods would work in physicians' own practice. Producing evidence-based data could take two more years, and the Workgroup was reluctant to wait that long.

- The recent FDA Influenza Vaccine Group raised a question about a study to show immunogenicity and efficacy as well as safety among very young children. Such a study

was proposed but not funded, leaving the evidence base thin. The NFID also held a workshop on the practical implementation aspects and found that some practitioners were immunizing infants this regularly with no problems. Dr. McMillan thought that pediatricians would be compliant and just need the recommendation to do it.

- In the interim before full recommendation, data are needed by the AAP and AAFP on whether the immunization actually influences hospitalization. The AAFP is heavily evidence-based and will ask for that. The data will set the stage for implementation and uptake.

- *Relevant experience.* The recommendation would benefit from evidence of the influenza burden leading to hospitalization, inclusion of some of the strategies proposed from the Rochester study (e.g., setting aside clinic time for vaccination, vaccinating at each opportunity presented), and relating the experiences of Rhode Island's parental acceptance of vaccinating 's 6-23 month old infants. Dr. Zimmerman reported preliminary data, in a Pittsburgh demonstration project targeting this vaccine to disadvantaged children, indicating a wide range (20-30%) of uptake in year one, but they still have trouble accomplishing dose #2. Some data should be available by the June meeting.

- The NIP issued an RFP to examine the issues related to risk communication and included solicitations schools of public health and the ATPM. They will survey family practitioners' current practices in the next few months and should complete a Medicaid survey by October. They will assess influenza vaccine effectiveness through the VSD, doubling the size of the previous Kaiser populations (16,000 participants) and hope to have more data by October. NIP also will retrospectively analyze hospitalization and outpatient outcomes over seasons. Nonetheless, there may not be much to say about strategies until a full recommendation is made.

- One opportunity to keep in mind is to advise standing orders for influenza vaccination of children, as is done for the elderly.

- The reason the vaccine was not licensed for <6 month-olds was because the licensure studies did not include those children. But there was also some evidence that the children aged <6 months receiving the vaccine were not healthy children. Dr. Singleton's review showed no evidence of adverse effects in the <6 month-old population.

  ACIP Response: There was no objection to the language proposed.

3. *Timing of the influenza vaccination*: On page 22-23, the rationale for tiered timing was added: prior vaccine delivery delays, that availability may be unknown until late summer/fall; and two rather than three vaccine manufacturers in 2003. The optimal time for vaccination, October - November, was cited. The Influenza Workgroup recommended adding those aged >50 years group to the vaccination in October or earlier, as well as for those aged <50 years at increased risk of influenza-related complications (including children aged 6-23 months), household contacts of high risk persons (including out-of-home care givers and household contacts of children aged 0-23 months. Vaccination of children aged <9 years should be given in October because they need a booster dose one

month late. Efforts to vaccinate other healthy persons aged 2-49 should begin in November. In that regard, two options to vaccinate were provided:

a. Option 1: If vaccination is requested in October, deliver it, unless delays or shortages of local vaccine supply exist or are expected; or
b. Option 2: If such persons request vaccination in October, deliver it.

Discussion included:

- This is a bit of an imponderable, since the seasonal situation changes annually. But the Influenza Workgroup wished to balance simplicity with flexibility for an unpredictable events. Dr. Neuzil suggested, in the Table 2 that practitioners are more likely to consult, combining September and October into one group, especially to maximize opportunities to vaccinate the elderly. But vaccination clinics should remain scheduled in November and December.

- A similar collapsing of November and December through March with a similar footnote was suggested, since this table does not discuss organized campaigns.

- Consideration is needed of those at high risk who cannot receive the vaccine at work because those campaigns are scheduled later. This is sensible if there is a supply problem, but such distinctions also may work against maintaining high coverage levels.

- To move rates from 70 million to 150 million by 2010, as wide as possible immunization periods will be needed. Aventis Pasteur got calls from practitioners after Thanksgiving ordering vaccine, when campaigns are normally thought to slow way down. People need to be reminded that vaccination in December and beyond is still helpful, and another 80 million patients will make practitioners already nervous about being swamped even more so. The text on timing should be moved up to page 8 from page 22. State that influenza season goes from October to March and the vaccination should be taken as early as possible. Making the timing complex lowers an already low priority for people. In addition, the reality is that even chronically ill patients do not visit their physician as regularly as they should. The windows need to be kept as wide as possible for providers.

- If Table 2 is retained, its title should be changed to "suggested timing" to be consistent with the first footnote; and/or as "recommendations when prioritization is necessary due to supply shortages".

- However, Dr. Orenstein related NIP's hope to institutionalize a two-tier system, even knowing this would be difficult for the first two years, to avoid the hostility resulting from the uneven distribution in 2000. Big vaccination campaigns have to be planned well in advance. This year, everyone is still waiting for the third strain to be determined, and if the reassortant does not perform as well, there may well be supply issues again. Tiers also are appropriate in a pandemic setting.

- Advantages to Option 2: There is no need to notify people if there are shortages; it reflects ACIP's thinking when the tiered system was created; and the Workgroup emphasized that

no one should be denied vaccination. The idea is to encourage people to seek the vaccine at certain times of the year, but not to turn them away.

- Disadvantages: Even with sufficient vaccine supply in 2002, distribution issues caused some to be delayed anyway. Perhaps there should be an Option 3, that being #2 with softer wording than "should not"; i.e., "vaccination may be given."

- In view of most of the committee's support of Option 2, Dr. Decker suggested adding a recommendation that organization campaigns not target low-risk populations early in the season. Aventis Pasteur will continue to follow its staged distribution program of the last 5 years, as though there could be a shortage, to ensure distribution is equal. And although the "all comers" baseline policy that if necessary would revert to tiers is attractive, this has never been done successfully, and the evidence indicates it cannot be done. CDC knew from Aventis in May 2000 that there would be shortages, but that information did not reach the field until the season was effectively over. Aside from that, a disruption is sometimes not apparent until late in September. He felt that plans cannot be based on a system that is predicated on getting a new message out.

- Dr. Tan recalled discussion of this at the summit. It was felt important to have a two-tier system as a foundation, and then, if in July or August an ample supply of vaccine is evident, an alert can be issued to recruit low-priority patients for October vaccination.

- A distinction is needed between the individual physician's vaccination and those of large campaigns (30-40,000 doses), which are planned months in advance.

- The recommendation would have to be restructured anyway, if there is a shortage, since this draft calls for vaccination of household contacts of those at high risk in September and October, which would pose serious implications to the supply.

- Table 2 could be customized, one to direct the individual provider to not turn anyone away and another to direct the organized campaign to not begin until November, similar to what was done two years ago during the shortages.

- Dr. Neuzil suggested changing the order so that the timing issue is in one area, moving up the paragraph on page 23 about scheduling campaigns after October, and noting that this will minimize the need for cancellation.

ACIP response: Preference for Option 2.

1. Miscellaneous additions, on pages 24-25, information was added on needle length for children from the General Recommendation; information on safety was added from a cross-over study of asthma patients, and additional VAERS safety data on children was provided. One correction to the draft in the meeting book (page 30) was regarding the vaccine supply. To the groups for vaccination in October, persons aged ≥50 years and children aged 6-23 months were added.

ACIP response: No objection.

2. *Standing order programs:* Text was updated to parallel the Final Rule issued by CMS in October 2002 which removed barriers to the use of standing orders for influenza and pneumococcal vaccination, and added coverage for Medicare/Medicaid providers participating in long term care facilities and hospitals and home health agencies.

Future Workgroup Plans. Over the summer, the Influenza Workgroup will develop supplemental recommendations on LAIV if it is approved by the FDA. The possible indications are in healthy persons aged 5-49 years and the vaccine will probably not be subject to tiered timing issues. Also to be discussed is a change to rank recommendations according to their evidence base in 2004.

Dr. Levin suggested adding to the text on page 21, regarding vaccination among those age 6-23 months, to address the existing (albeit limited) evidence of efficacy. That was agreed, although "primary changes" may not be the best area in which to add it. That will be discussed.

Dr. Zimmerman **moved that ACIP adopt the influenza statement as presented for 2003-04.** Dr. Hanson seconded the motion.

Vote:
In favor: Offit, Levin, Zimmerman, Word, Modlin, Salamone, Hanson, Brooks, Birkhead, Tompkins
Opposed: None
Abstained: Rennels

The motion passed.

HIV VACCINE
HIV Vaccine Workgroup Chair Dr. Gus Birkhead reported that this Workgroup was formed in the fall of 2002 to address the issues related to development of the HIV vaccine. Its 18 members include five ACIP members and representation of the NIP and NCHSTP, federal agencies, state health departments, HIV clinicians, academic and medical institutions, and importantly, community representatives. A conference call was held in November 2002 and the first formal meeting was held on the previous day.

The announcement by VaxGen on the preliminary results of their Phase III trials of an HIV vaccine in humans altered the first meeting's agenda. VaxGen presented their results by telephone and the group discussed them. In addition, background presentations were provided on immunology, and CDC reported a on the use of a partially effective HIV vaccine, including modeling of its impact on the epidemic. A partially effective vaccine may require some retuning of the ACIP's traditional approach to vaccines of only modest efficacy. And finally, the Workgroup had good input from the two community representatives, hopefully the beginning of a good two-way communication.

The Workgroup's charge is to: 1) review the current status of HIV vaccine research (vaccines in development or trials, developments in the field); 2) familiarize the Workgroup members with challenges to vaccine development and related strategies; 3) review CDC's plans and guidance

on potential use of vaccines in the U.S. and present responses/options to the ACIP; 4) assist CDC in responding to the results of efficacy trials; 5) familiarize Workgroup members with the likely many implementation issues for any approved HIV vaccine in U.S.; and 6) provide a liaison to the UNAIDS HIV Vaccine Advisory Committee and other HIV vaccine groups.

The challenges to the development of a successful HIV vaccine include that prevention is needed of an infection whose risks are primarily behaviorally determined. That could lead vaccinees, believing in their greater safety, to increase their risk behavior and actually increase HIV transmission. So, HIV vaccines need to be delivered in the context of an integrated prevention program. Immunologic challenges include that HIV directly attacks the immune system, that the correlates of protection are unknown, and that different efficacy endpoints than just disease prevention may be possible (e.g, prevention of disease or secondary transmission). And, the fact that the populations impacted by HIV may lack access to services, be marginalized or stigmatized, highlights the importance of involving the affected communities to ensure trust in the recommendations.

Phase III Efficacy Trial of AIDSVAX B/B

Introduction. Dr. Lance Gordon, Chief Executive Officer of VaxGen, introduced the presentation of their Phase III study data, emphasizing its very preliminary character. Much more analysis will be done and data generated. The trial included 5400 volunteers, who provided >14,000 evaluable patient years and who received 35,000 injections. A total of 70,000 serum samples were collected. The principle assays done to date were the samples from the infected individuals; only 5% of the uninfected samples have been analyzed. Supported by NIH funding, they also collected two samples of lymphocyte cells from each volunteer (the total exceeds 10,000) at different time points, which will allow further exploration of genetic background. The study database holds over 800,000 case report forms, so much more analysis is to be done. Only a week's worth of analysis has been done to date, mostly for primary efficacy.

Trial Presentation. Principal Investigator Dr. Vladimir Popovic then detailed the design, process and outcomes of the trial. The AIDSVAX B/B efficacy trial in North American and the Netherlands was conducted at 59 local sites in collaboration with CDC and NIH. This study followed 5108 men who have sex with men (MSM) and 309 high risk women. They received seven doses of the AIDSVAX B/B vaccine with two antigens, MN+GNE8, at 0, 1, and 6 months for the primary series and then at 12, 18, 24, and 30 months. The ratio of vaccine to placebo cohorts was 2:1. The participants were followed over 36 months with serology done every 6 months to diagnose infection.

Trial Design

- *Definition of infection* was a positive EIA which was confirmed by Western blot. The date of infection was assigned to the midpoint of the first positive and last negative specimens, which were run using the highly sensitive nucleic acid test (NAT).

- *Follow-up.* After infection, the volunteers were followed and viral loads were measured at the subsequent <1, 1, 2, 4, 8, 12, 16, 20 and 24 months. Antibody titers were taken at baseline, before each immunization and two weeks after.

- *Inclusion criteria* for the MSM were those who had any anal intercourse in the past 12 months. MSM were excluded who were in a continuous monogamous sexual relationship for >12 months with the same male HIV-negative partner. The inclusion criteria for women were those who: 1) were currently (within 30 days) in a sexual relationship with HIV+ male partner; or 2) had 5 or more male sexual partners within the past 12 months; or 3) exchanged sex for drugs or money in the last 12 months; or 4) smoked crack cocaine in the last 12 months.

- The *primary endpoint* was prevention of infection. The risk of HIV infection in vaccine recipients was compared to the risk in placebo recipients, which was expressed as 1 minus the relative risk times 100%. A discrete failure-time regression model over 36 months was used with each six-month period individually examined.

- The *secondary endpoints* were:
    - Reduction of viremia, judged by comparison after infection of pre-ART plasma RNA measurements of the infected placebo recipients versus the infected vaccine recipients; and the time to ART or viral thresholds of 1,500; 10,000; 20,000; and 55,000 copies/ml.
    - The suppression or reduction of detectable viremia (aviremic infection), judged by four levels of plasma viral load, from 10,000 copies/ml to below the level of detection (< 400 copies/ml) for at least 12 consecutive months.
    - The *third endpoint* was slowing disease progression as measured in change of CD4 counts over time, measured by a comparison of the CD4 measurements pre- and post-ART, of the infected placebo recipients versus the infected vaccine recipients, after infection.

- *Trial cohort design* was done with FDA and included: all those immunized for safety analysis (5417 placebo and vaccine); an intent-to-treat cohort (5403 receiving ≥1 dose), and a weighted cohort (5009 receiving ≥3 doses and not infected by the third dose, to judge vaccine efficacy). The cohort percentage that completed the trial was 83% in the placebo group and 84% in the vaccine groups.

- The *demographics* of the placebo/vaccine groups were outlined: a median age of 36 years for both vaccine and placebo groups, 94% male and an average of 5.7% female; ~82% white, 7% Hispanic, 6% black, 1% Asian and 2% other.

- The *baseline risk* was assessed six months before enrollment for number of HIV+ partners, unprotected anal sex with the latter, unprotected anal receptive sex, and unprotected vaginal sex for women. The results for both placebo and vaccine groups were virtually identical.

- Similarly, the *risk behaviors* over 36 months (of unprotected anal and anal receptive sex, as well as sex with an HIV+ partner) tracked well between the two cohorts. Risk reduction counseling was provided every six months to all volunteers. A chart showed a slight decrease in the first six months which then leveled through the 36 month follow-up.

Safety Assessment

The most common reactogenic symptoms three days after injection in the placebo versus vaccine groups, respectively, were:

- Local reactions (84.6% placebo, 91.7% vaccine, respectively); pain (81.9% and 89.8%), erythema (19.8% and 35.9%); edema (17.0% and 32.9%); induration (14.7% and 29.2%); and site nodule (11.7% and 20.6%)
- Systemic reactions (pre-specified events reported within three days of immunization) were reported by 63.8% and 68.4% of the placebo and vaccine groups, respectively. These were headache (35.3% and 38.8%) and rash (3.6% and 8.0%).
- Two possibly related vaccine-related serious adverse events of cellulitis at the injection site were reported in the vaccine group, but that was not repeated in subsequent immunizations. No infecting agent was found and the events resolved in a few days with a minimal treatment.

Vaccine safety conclusions. No differences were seen in either adverse events or serious adverse events between the treatment groups. There was no evidence of enhanced susceptibility to infection nor evidence of increased progression of HIV among infected vaccinees.

The *annualized HIV incidence rate* on which the trial was designed and powered was 1.5% in the placebo group. However, VaxGen found double the incidence than expected: 2.7% overall (CI of 2.3 to 3.2); 2.8% for males and 1.5% for females, per 100 person years of follow up.

Vaccine Efficacy

Vaccine efficacy (VE) was presented overall by race, age and by risk groups, for the 95.12% confidence interval. The latter was derived from the penalty because the analysis is incomplete; 18 months is required for complete analysis. The chart of trial results is presented on Attachment #2.

The overall trial did not show protective efficacy (3.8%) to HIV in the weighted cohort and a negative efficacy (-9.7%) was shown for the White/Hispanic cohort. However, surprisingly, efficacy rose to 66.8% for the Black/Asian/Other group (78.3% for the black group, 68% for the Asian group, and 46.2% for the Other group). For men overall, VE was 0.7%, but was 59.5% for the blacks/Asians/others group and -8.8% for whites/Caucasians. The small numbers of women enrolled prevented calculation of VE, but those results reflected 86.4% for all volunteers. Infection occurred in 4.3% of the placebo group and 0.6% of the vaccine group. A black/Asian/Other group showed a similar trend to the men in that none of the vaccine group was infected while and 1.3% of the white/Hispanic vaccine group was; 7.3% of the placebo group became infected. Dr. Popovic noted that, although the numbers are small, the three-year term and high follow-up seem to support the indication of a similar trend. Further analysis will be done of these data for correlates of protection, using eight antibody assays and molecular sequencing of the viral envelope.

The *time to HIV infection* for whites and Hispanics showed a close parallel between the placebo and white and Hispanic group, but a longer time to infection in the vaccine group than the placebo group among the Black/Asian/Other group. No data on the secondary endpoints were presented due to insufficient analysis in the week since analysis began.

Plans for Correlates of Protection Analyses

Immunogenicity: Analysis will be done of a sample which was pre-selected at the beginning of the trial. The last negative test prior to infection of 5% of uninfected vaccinees and 1% of the placebo group will be compared to infected vaccinees. Eight antibody assays are planned over the entire gp120: MN/GNE8 gp120; MN V3; GNE8 V3; MN V2; GNE8 V2; Inhibition of CD4 binding to MN-rgp120; Inhibition of CD4 binding to GNE8-rgp120; and MN neutralization.

Molecular sequence analysis of the viral envelope will be done on a full length gp120, sequenced in 350 of 368 infections (18 were excluded due to undetectable viral loads or insufficient viral isolates). S^3 analysis (subtype, subclass, and sieving) will also be done.

Preliminary results of the *subtype* analysis showed all to be subtype B except for one subtype C in Amsterdam who had traveled to Asia at the time of infection. No subclasses were identified by phylogenetic analysis. The *sieve* analysis indicated that the frequency of MN-like viruses was lower than expected, at ~47%, rather than the 66% of MN-like viruses in the vaccine antigens. However, the preliminary sieve analysis indicate again the trend of apparent sieving in non-whites and blacks, Asians and others.

Preliminary study conclusions were that the vaccine's efficacy was not demonstrated among Caucasians (whites/Hispanics), but protection was demonstrated among non-Caucasian groups (blacks, Asians, others). There was an apparent correlation with MN-neutralizing antibodies. Full analysis is still in progress. Additional data may be able to be obtained through continuous follow-up of the volunteers and the stored specimens. The second, Thai, trial with a similar vaccine will be complete later in 2003.

Dr. Gordon added that they are already seeing relationships between neutralizing antibody titers and infection prevention with only 5% of the samples analyzed. In the next steps, they will complete analysis of the currently available data and review it with the FDA. They will present more of their data and analysis at the impending Keystone scientific conference, hopefully with a better understanding of the differences between the subpopulations. And with FDA, CDC and others, they will map out additional studies that might be necessary.

HIV Workgroup Response. Dr. Birkhead summarized the Workgroup's discussion on the previous day, after a similar presentation from VaxGen. The Workgroup recognized the importance of the completion of the world's first HIV vaccine Phase III efficacy trial, but noted the very preliminary nature of the available results, and that they showed no overall efficacy of the vaccine. The unexpected apparent protective effect among blacks, Asians, and other minority groups emerged from a small number of blacks and minorities in the trial, and the results were based on small subsets. That can be misleading.

The Workgroup was cautious about drawing final conclusions at this point. They asked, when presented to the media and the public, for an emphasis that the results are preliminary in nature, and they should not be overstated. There is an immediate need for rapid additional analysis of the trial data, especially of the behavioral and antibody level data in relation to infection. Behavioral data could be supplemented by data on receptive anal intercourse by women. CDC's representatives on the Workgroup appreciated having been involved in the analysis sessions. VaxGen's continued collaboration with CDC in the data analysis was encouraged by the Workgroup. They found it premature to decide on the need for further clinical trials. To

maintain the public's trust, they urged DHHS/CDC to ensure that clear messages are delivered to the public, particularly to the HIV community, about the meaning of the results and further plans.

Discussion with Drs. Popovic and Gordon included:

- *Does VaxGen have a hypothesis for the different efficacy in the racial groups, or is it a statistical anomaly?* The first hypothesis is that immune responses (e.g., neutralizing antibody) in blacks, Asians and others may be responsible. But although the numbers and further analysis is needed, a statistical anomaly was ruled out. *So there may be a correlation between neutralizing antibodies and protection. But why in one and not another racial group?* VaxGen is now looking at eight different assays; perhaps others could help to characterize the immune response, and they may also look for genetic markers which, for other antigens, are known to pose immune responses. But this does not seem to be an artifact; it seems to relate to race. Examination of demographics did not show any differences between racial subgroups regarding education, SES, sex, or geography, etc.

- *How was the decision made to combine Hispanics and whites?* Originally, they were separate, but the most recent guidelines for ethnic/racial subgroups changed and they were combined on the suggestion of experts and CDC at the time of analysis. But when Hispanics were combined as minority group, the statistical significance of the data were same.

- *Are you saying that the responses were quantitatively lower in blacks than in Caucasians and Hispanics?* Again only 5% of samples have been analyzed, but they show a trend of vaccine protective activity in neutralizing antibody levels, aviremic infection, low viral levels, higher CD4 counts, and in the molecular sieving. The statistical and medical significance remains to be seen, but these results are consistent. *Were there any with no response?* No, nearly all individuals produced antibodies after 6 doses.

- *The SIV data with antibody prophylaxis, the height of antibody levels, and the homology of the infecting/challenge strain and the vaccine strain is impressive. But the study shows only neutralization against MN, the vaccine virus strain. Are there virus isolation possibilities with those specimens? The ideal would be to match the infecting virus with the antiserum from the same patient; or, to use a current isolate for utilization studies.* The gp120 was sequenced in every isolate regardless of subgroup, vaccine or placebo. The molecular sieving looked at what strains were impacted by the vaccine, and the vaccine impacted strains closely related to GNE8 or the MN, changing them proportionally. Additional data on the distribution of HIV types and subtypes will be issued. *Dr. Plotkin emphasized that VaxGen should not depend solely on sequencing; neutralization is a complex phenomenon.* Agreed, but the vaccine contains only gp120. Other antigens may have role in protection, but the analysis to date has only looked specifically at gp120.

- *Can the demographic work also examine a probable mode of transmission, specifically, injection drug use?* Injection drug use in the last three years was an exclusion criterion; <1% of the participants reflected that. The primary risk factor was sexual transmission.

Dr. Birkhead stated that the HIV Workgroup will continue to meet, and VaxGen will be on the next agenda.

SMALLPOX

CDC Smallpox Program. Dr. Ray Strikas updated the committee on the smallpox vaccination program's (SVP) organization, progress to date, and program evaluation.

The President's plan for civilian smallpox vaccination program, announced in December 2002, had four components, to: 1) vaccinate smallpox response teams, 2) vaccinate DOD personnel, 3) vaccinate selected staff in overseas assignments (e.g., State department staff). Finally, 4) vaccination of the general public was not recommended, but methods with which to accommodate those who insist upon it were to be explored.

Team composition. The Smallpox Public Health Response Teams are composed of the public health and medical personnel needed to investigate initial suspected cases and initiate control measures. This includes medical, public health, epidemiologic, laboratory, and nursing personnel, vaccinators, and others. The Smallpox Health Care Response Team will be identified by state and local public health in collaboration with hospitals. This is a voluntary program in which healthcare personnel from participating hospitals will evaluate, manage, and treat the initial suspect/diagnosed cases.

In the civilian sector, the Smallpox Vaccination Program (SVP) will: provide vaccination and follow-up service to responders; enhance community awareness and clinician expertise regarding smallpox vaccination; conduct disease (rash illness) surveillance and laboratory analysis to detect cases of smallpox and subsequent cases; implement public health interventions (isolation/quarantine; and prepare a cadre of vaccinated responders ready for wide-scale vaccination if necessary.

The key SVP components are pre-screening, state and local program support, data management, evaluation, vaccine safety, and education and training. The ACIP also has formed a Smallpox Vaccine Safety Monitoring Workgroup to monitor the SVP's communication, surveillance and research activities.

The pre-vaccination packet previously presented to the ACIP is on CDC Web site. New materials added are a household contacts information sheet (an IOM recommendation); record keeping guidelines; an outline of the whole program and additional materials from states (HIV screening, additional exclusions from vaccination, etc.),.

The vaccination process allows for an opt-out ability at least three times: on review of the pre-vaccination packet; upon finding a contraindication, HIV or pregnancy testing; and upon the final clinic review of the above. State and local public health support is critical. A teleconference held 3-4 times per week is now reduced to twice a week with program progress. CDC is collaborating with FDA on package label/IND issues and with DOD and DVA to learn from their programs, as well as with ASTHO, NACCHO, and the APHL (Association of Public Health Laboratories).

Program evaluation studies are to begin soon (hospital participation, non-participation; knowledge, attitudes and beliefs of primary care providers; funding sources, etc.). Surveillance is being set up for needle sticks, site care evaluation, and lab evaluations.

Current status: As of the previous Friday, 7355 individuals have been vaccinated nationally. Of those, 3287 are public health personnel, 3472 are healthcare personnel, and 595 are "other" (e.g., federal employees stationed in states to be part of their public health response). At least one employee is vaccinated in 488 hospitals, about 10% of the U.S.' acute care hospitals. As of February 21, 2003, >270,000 doses of vaccine had been delivered to states. Some states had not yet reported their start date for this program.

CDC has 62 grantees for bioterrorism preparedness and their plans were approved for all states, the District of Columbia, New York City, Chicago, Los Angeles county, Palau and Puerto Rico. They projected, as of December 31, 2002, that 1101 public health teams with 19,629 people will be vaccinated, as well as 4532 healthcare teams with 396,062 persons identified as potential vaccinees for the latter.

Training. CDC is working with its partners in training and education and has conducted nine training/education sessions. Through February 17, 58 training products were available. Training has been done over satellite broadcasts, by CD ROM, Internet, and classroom.

Program reporting: Weekly reports are requested from the projects regarding vaccination totals by public health and healthcare teams and other; number of hospitals with ≥1 person vaccinated; and take rates to vaccination. The progressive vaccinia data management system is being implemented as the reporting engine to monitor vaccine shipments, training activities, vaccinations, and adverse effects reporting. CDC's Website will report the weekly vaccination number by states and report adverse event counts.

The DHHS Secretary, on January 24, 2003, issued a declaration on the administration of smallpox counter measures, including VIG and Cidofovir. It provides liability protection for participating hospitals and public health participating in the SVP, although there is not yet a uniform compensation program. DHHS/CDC continue to work aggressively with OMB and Congress to address these issues. States/programs across the country have state compensation programs, but these are not uniform across the country.

Program guidance is being developed for the evolution of the SVP and bioterrorism response preparedness, to be issued by March 15. CDC is evaluating how best to establish a program with IND vaccine for the public that insists on receiving it, and is improving its monitoring and reporting capacity.

DOD Smallpox Program Dr. John Grabenstein, of the DOD, reported on the military's smallpox vaccination experience. They have vaccinated almost 10,000 hospital and health care workers. The entire DOD program has vaccinated >250,000 individuals, about two-thirds primary and one-third revaccinees. The adverse events profile reflects ~3% of vaccinees needing a day or two of sick leave. They have had two cases of encephalitis and several of myocarditis. From an infection control perspective 12,000 worker months of patient contact have produced no transmission of vaccinia in healthcare settings, despite the fact that many people are sited in

places with very few washing machines (e.g., Afghanistan). That, and very few cases of autoinoculation, supports that it is difficult to autoinoculate with vaccinia.

ACIP Vaccine Safety Monitoring Workgroup. Dr. Modlin reported that a Vaccine Safety Monitoring Workgroup was formed by ACIP on CDC's request, in late 2002. Three members regularly attend from ACIP (himself and Drs. Birkhead and Siegel), as well as 4-5 members of the Armed Forces Epidemiology Board and six other members. The purpose of the workgroup is to evaluate smallpox vaccine safety data as it is received weekly from federal smallpox programs and the DOD program. They also are functioning as a DSMB for the VIG and Cidofovir programs, both of which are administered under IND. This is the workgroup's first formal report to ACIP. It will also report to the IOM and the Armed Forces Epidemiology Board. CDC staff provide individual and aggregate safety data and adverse effects investigation data. The Workgroup meets on Fridays by conference call.

The Workgroup's focus to date has been to review the early data, such as Dr. Grabenstein presented. They began work with development of a standard definition of adverse effects. Many of the terms used for adverse events in the historical literature are confusing and often overlap, especially for generalized rashes; so they will try to standardize case definitions for monitoring purposes. They also will attempt to define the rates of adverse effects considered unusual and potentially serving as trigger points, to advise CDC about changes in smallpox program direction. They will begin with the states' data and that of national surveys 30-40 years ago, despite problems in extrapolating from that, to help create definitions for the current program. What has not been done so far is to present any adverse effects information in any detailed way.

Discussion with Mr. Strikas included:

- *Where do we stand in terms of vaccine availability and distribution if there is a case within a week?* There are 15 million undiluted doses of Dryvax and there are 80 million doses of the Aventis Pasteur vaccine that could be used in an emergency, diluted 1:5 to produce 50 million doses. The Acambis products are being evaluated in various trials. They will be available in hundreds of millions of doses in early 2004 but are being produced now and in an emergency could be available. The supply is ample. Dr. Midthun reported that NIH has been evaluating the Aventis Pasteur product to verify that it could be used by CDC under an IND if needed. Dr. Heilman reported the vaccine as performing as well, as if not better, than Dryvax. All 62 grantees' plans are under review; and there is a good supply of vaccine in the states. That can be supplemented within 12 hours from the NPS, and moved across the country within 5 days. CDC is also evaluating its own diagnostics and surveillance components to improve its response plan in the event of outbreak, building on the experience of rash illness surveillance of the last 10 months. A variety of things are being codified in the revised CDC plan as well as with state partners.

- *How may doses were sent to the states?* 275,000 doses were requested and shipped to states, based on their projections to vaccine their staff, but the amount used may differ. To date, several states have reported vaccinating less than the anticipated volunteers, in part due to the unclear liability issue. Four states probably account for half the 7,000 vaccinations provided to date. Although the states know that the hospitals, acting as an agent of the federal government, are protected under the federal Liability Tort Claims Act, the uneven

levels of worker compensation across the country remain. That is being addressed by Congress now.

- In New York, state/local level staff have been diverted to work on this. Public health began vaccination first and then will fan out to vaccinate in hospitals and then offer public vaccination. The program is occurring in a very phased fashion. Compensation is the key problem and is not addressed in the National Security Act. New York sets this individual-by-individual, but it is capped at ~$40,000/year and still requires going through a legal process to receive compensation.

- *NIH is not proceeding with vaccine trials in children. Given that, if an event occurred next week, is there a protocol for use of smallpox vaccine in children? Should they be excluded if they have the listed immunocompromising conditions (e.g., eczema)?* There are no answers. The general principle is that if there is an outbreak and a person is exposed, there will be three punctures for primary vaccinees and 15 for revaccinees. CDC would like to make that uniform. But there are many unknowns; an IND is needed for use with the Aventis or another vaccine is deem appropriate for post-event response. Much work remains to be done.

- Dr. Baker registered the AAP's official protest at policy that does not include study among children. They must be considered now. Dr. Midthun added FDA's strong support of including children in trials for the vaccine indication. The current ACIP recommendation also calls for vaccination for all ages in the event a case is identified.

- *So, if post-event widespread vaccination has to be done, the Wyeth's 1:5 dilution would be used, but this has not been studied in children. Would not the undiluted vaccine have to be used among children?* Dr. Linda Rotz, of NCID, reported that there is no age differential in the protocols used over the years for a post-event setting. The 1:5 dilution applies to the Aventis product as well as for Dryvax. None of the INDs have an age restriction, although they still have the same contraindications for children as for adults (e.g., eczema). But Dr. McMillan pointed out that it is not known if the 1:5 dilution is appropriate for children. Dr. Heilman confirmed that there have been no studies of children with 1:5 Aventis Pasteur or Dryvax. The proposed protocol to study that was referred to DHHS due to the risk benefit ratio. Dr. Gellin had nothing further to report on that, but recalled that the current policy was also based in part on the pragmatic fact that if the Dryvax supply had to be used, there would not be enough for general use subsequently.

- Dr. Neal Halsey, one of the ten reviewers of the NIH protocol, normally supports including children in studies. But in this case, different thinking is required when there is more than a minimal risk in giving it to children. There is no known risk from smallpox, so there is no benefit. Some generalizations could be made of what is learned in adult studies; if it works well in adults, generally it is as good or better in children. He encouraged a few ACIP members to form an ad hoc workgroup to read all of the reviews before recommending that these studies be done in children, to determine what questions need to be answered and how many children should be put at risk from a vaccine that may not provide a real benefit. He offered to assist that workgroup as needed.

- *Are there plans to study the new tissue culture vaccinia vaccines in children?* Mr. Ken Bush, of Baxter, Acambis' partner in developing that vaccine, confirmed planned pediatric trials for the Vero cell vaccine.

- Dr. McMillan advised that great clarity be ensured that extrapolation was done to children from the adult experiences, if it must be used before pediatric issues are resolved. Very specific protocols for vaccine use in a post-event situation will be needed. This is a task for the Red Book Committee, in coordination with CDC and local health departments.

- *Some Virginia tertiary centers have refused to participate, fearing transmission to patients. Are there comparable DOD facilities included in the 12,000 worker months with no transmission?* Dr. Grabenstein reported that DOD has a full spectrum of facilities offering services, including tertiary referral centers which report regularly. Clinical manifestations seen to date included vaccinees with chest pain, who were treated symptomatically in hospital and then discharged 3-4 days later and fully recovered. Finnish data on patients also showed no sequelae a year later.

- However, Mr. Salamone observed that, since military and medical care workers are in a more controlled environment, safety issues may not be reflected in the adverse effects data now being collected. Dr. Modlin reported passive methods being used to monitor those (VAERS and enhanced VAERS) as well as active surveillance. The ACIP Safety Committee was comfortable with the current monitoring plans, and hoped to obtain better greatly improved data than in the past due to the nature of the surveillance.

- Dr. Gordon reported a cold-adapted pediatric smallpox vaccinia vaccine developed and licensed in Japan in 1980. They are scaling up for manufacture and Baxter is working with them to import the vaccine. The data showed a lack of neurotropism, no CNS effects, markedly improved safety (e.g., smaller blisters and pox size), and a 95-97% take rate. The WHO neutralization test showed equal or better neutralization activity than the parent Lister strain.

- *How many cases of myocarditis occurred and what was the severity of the two cases of encephalitis?* Dr. Grabenstein reported four cases of myocarditis, a rate of <1 per 50,000; the Finns had a rate of 1:10,000 in their case series. One case of encephalitis had a nine-night hospital stay; the other required a 2-night stay. There were some questions of whether the latter should be called encephalitis or encephalopathy with delirium

Civilian Safety Monitoring Activities

Dr. Eric Mast, of the NIP, reported on CDC's civilian safety monitoring activities. Its objectives are to: 1) monitor the occurrence of adverse effects associated with vaccination (that expected based on previous experience and that not expected); 2) monitor the effectiveness of contraindication screening and identify any need for new contraindications; and 3) facilitate timely and appropriate distribution of VIG/Cidofovir to the civilian population.

IOM Program Review/Recommendations. CDC contracted with the Institute of Medicine (IOM) to review the SVP. In January 2004, the IOM Committee on Smallpox Vaccination Program

Implementation strongly recommended that CDC conduct active surveillance, rather than relying on existing programs. All vaccinees and their contacts should be followed for: 1) adverse effects that require hospitalization or outpatient care; 2) unidentified contraindications to vaccination among vaccinees or their contacts, or 3) vaccinia transmission to contacts. A telephone survey of ~10,000 vaccinees will be conducted 10-21 days after vaccination to identify common, non-serious events.

Implementation of this system will rely on several components:

- The *vaccination clinic staff* assign a vaccinee identifier and enter vaccination information into the electronic tracking system (CDC's or the state's).

- The *site care monitors* assess site care vaccine take, signs/symptoms of possible adverse effects, determine fitness for duty (hospital staff), and report any adverse effects associated with vaccination as they occur. When follow-up is completed (21-28 days) they ensure that information is collected on the three areas recommended by the IOM. CDC is providing a Web-based data entry mechanism to document this information.

- *Clinician*s report adverse effects associated with vaccination to state health departments and VAERS. Those needing assistance with evaluation of vaccinees with potential adverse effects should contact their state health department or CDC's clinician information line. The smallpox vaccination adverse effects that are recommended for VAERS report are listed. Serious adverse events (e.g., resulting in hospitalization or disability) are to be reported to the FDA.

- *State health departments* will have a Smallpox Vaccination Adverse Effects Coordinator, who establishes and coordinates state smallpox adverse events reporting and tracking systems; identifies and tracks selected adverse effects in collaboration with CDC (case investigation to verify diagnosis and to monitor clinical course/outcome; facilitate VIG/Cidofovir release; assist with submission of VAERS reports; and facilitate training/communication with clinicians responsible for adverse effects reporting and management.

- *CDC*'s role rests in the Smallpox Vaccine Adverse Events Monitoring and Response Activity of NIP's Epidemiology and Surveillance Division. Its has three teams. The *Clinical Consultation Team* provides 24/7 consultation for adverse event calls referred from the clinician information line, active tracking of adverse events with state health departments, and VIG/Cidofovir release as appropriate. The *State Technical Assistance Team* provides technical assistance to states through the Smallpox Adverse Events Coordinator, mostly through weekly conference calls. And the *Adverse Events Surveillance Team* monitors VAERS reports and selected reports that are not followed up upon by the clinical consultation team.

The Epi-X secure data system provides communication and oversight of the data and rapid information exchange between health departments and CDC. The data are compiled regularly and reported in *MMWR* as well as the CDC smallpox web site. The ACIP Workgroup evaluates those data, as reported by Dr. Modlin. The IOM provides ongoing programmatic evaluation.

SVP status to date. To date, 7354 civilians vaccinated. The adverse events are reported according to three categories, whose status as of the previous Monday was provided: 1) life threatening events (e.g., eczema vaccinatum, fetal vaccinia, etc) – none reported to date; 2) moderate to severe events previously associated with vaccination (e.g,. generalized vaccinia, ocular vaccinia, etc.) – one suspected case of generalized vaccinia was to be reported in the next *MMWR*; and 3) other events of concern, which include other serious events (according to the FDA definition), non-serious events, and VIG release and transmission to contacts. There have been 23 non-serious adverse events reported. One, a myocardial infarction in a man with coronary artery disease, was to be reported the coming week.

Discussion included:

- *Are most of these 7000 vaccinated individuals revaccinees?* They are a combination of primary and revaccinations. There is no breakdown on percentages; that needs to be done. But probably most are revaccinees since the programs are beginning with them. The age of the individuals' of the two events (39 and 60) suggest that both were revaccinees.

- *Reportable events should list myocarditis/cardiac problems distinctively, not as "other", since they are already being seen among revaccinees.* They will be separately identified as an event requiring hospitalization or outpatient care. A VAERS report will be filed with specific information including the diagnosis of myocarditis. But this may deserve its own line/category in *MMWR*. The Workgroup discussed this as well, considering the military experience, and also discussed another possible adverse effect from inadvertent vaccination of susceptible persons (e.g., pregnant women or those immunocompromised).

Use of VIG in an Inadvertent Vaccination Setting

Dr. Strikas introduced the next presentations, in the context of the committee's consideration of the possible benefits of using VIG. There are currently INDs for treatment of adverse events with VIG, but none for prophylactic use.

***Use of VIG Among Pregnant Women After Inadvertent Vaccination*.** Dr. Susan Goldstein reported that fetal vaccinia is a rare event. The 47 cases reported in the literature are probably under-reports, since it is less likely to be recognized in undeveloped countries and its presentation can be atypical (e.g., no skin lesions).

Conflicting data have been reported regarding vaccination and increased risk of spontaneous abortion or miscarriage. There are data on 24 of the mother/infant pairs in these 47 cases. Ten of the mothers were primary vaccinees and three had been previously vaccinated. Two were contacts, one was never vaccinated and the other was previously vaccinated. All three trimesters of pregnancy were involved in the fetal vaccinia seen. It was more common in the first and second trimesters, since pregnancy is more obvious in the third trimester and vaccination is more likely deferred. The pregnancies produced 25 fetuses, 11 lost in spontaneous abortion or miscarriage and 14 live births, of whom 10 infants died.

Three cases of fetal vaccinia have been reported of the New York City Board of Health (NYCBOH) smallpox strain, the U.S. strain. One woman was a primary vaccinee, another was a revaccinee but had a take for the first time; the third woman's vaccination status is unknown.

They were all vaccinated in the first or second trimester and there was one fetal death. One of the two live births lived.

CDC estimated the risk of fetal vaccinia based on the data from the New York City outbreak (NYCBOH vaccine strain — zero per 170,000 vaccinated pregnant women) and the Scotland/Wales outbreak (Lister vaccine strain – 1 per 10,000-12,000). The routine vaccination program data indicate a risk of 1 per 90,000-280,000 vaccinated pregnant women, but also 1 per 5,600-17,000 primary vaccinees who are pregnant.

Etiology. The theory that maternal viremia leads to infection of the placenta and the fetus is supported by placentas examined from fetal vaccinia cases. The frequency of fetal vaccinia may be strain dependent. There are few data, but two studies have indicated no virus detected after vaccination with the NYCBOH strain, while viremia has been documented with some of the "hot" European vaccine strains. More sophisticated lab methods may detect viremia more frequently.

If inadvertent vaccination of a pregnant woman does occur, vaccinia immune globulin (VIG) could be administered to prevent viremia in the woman and therefore infection of the fetus. But again, there are few data to support this action; those available are only descriptive and inadequate to determine if VIG is efficacious in preventing fetal vaccinia or fetal outcomes.

The remaining option to determine if VIG should be offered to pregnant women is to do a risk assessment of the adverse outcome versus the risk of VIG. Even the NYCBOH strain poses risk to the fetus, but there are no data to indicate if there is an increased risk of spontaneous abortion and miscarriage. And, although any drug poses risk, and VIG's efficacy is unproven, it is relatively safe. In the past, VIG administered IM was assigned to pregnancy category C; there are no data on VIG administered by intravenously. IVIG is used to treat many medical conditions, including those occurring during or due to pregnancy (e.g., ITP of pregnancy, recurrent miscarriage, and anti-phospholipid syndrome). IVIG is a pregnancy class C drug. There are also specific hyperimmune globulins occasionally used in pregnancy (e.g., varicella zoster immune globulin for susceptible pregnant women exposed to persons with chickenpox. Anti-D is given to pregnant women (e.g., RhoGAM), and all the specific immune globulins are pregnancy Class C.

An adverse reaction to IVIG occur in 1-15% of pregnant women. The symptoms are usually mild and self-limited (headache, myalgias, light-headedness, nausea, vomiting) but also can be more severe (pyrogenic reactions, vasomotor/CVS disruption, anaphylaxis, aseptic meningitis, hypersensitivity reaction, and acute renal failure). Data from the clinical trials of an IV VIG, Cangene, recently licensed in Canada specifically for use in pregnant women, showed mild adverse reactions among the 60 participants, but there were no pregnant women among them.

Fetal vaccinia or another adverse fetal outcome would be a tragedy individually, but also nationally, in terms of lost confidence in the both the smallpox and routine vaccination programs and other public health programs. Among the practical considerations of administering VIG to pregnant women are the time after vaccination (viremia probably occurs 7-10 days afterward); the dose of VIG (probably one dose); the trimester of pregnancy; whether vaccination is primary or a revaccination (fetal vaccinia is more common with the primary vaccination or remote

revaccination); whether the woman is a vaccinee or a contact; and, if contacts are included, how that is defined and under what types of circumstances.

Estimated Risk of Fetal Vaccinia. A chart was presented of the estimated risk of fetal vaccinia based on outbreak data. The calculation assumed a U.S. birth rate per 1000 population for each given year applied, a population-based vaccination distribution that included pregnant women (in view of the outbreak setting) and poor recognition of fetal vaccinia as a potential adverse outcome.

- U.S., 1947 (NYCBOH strain): 6.5 million vaccinated, potentially 175,000 pregnant women. Outcome: no fetal vaccinia. Risk: 0:175,000.

- Scotland, 1950 (possibly Lister strain): 500,000 vaccinated, potentially 12,000 pregnant women; one fetal vaccinia case. Risk: 1:12,000.

- Wales, 1962 (Lister): 900,000 vaccinations, potentially 20,000 pregnant women; 2 fetal vaccinia cases. Risk: 1:10,000.

- U.S. routine program, 1967-1971: 65 million vaccinations, potentially 11 million given to women of reproductive age, 650,000 of them primary vaccinations; only one known case of fetal vaccinia. Risk: 1:11million. The fertility rate was assumed to be 85.9 per 1000 women aged 15-45 years. Assuming that pregnant women were vaccinated between 10-30% as frequently as other women the same age, and given known contraindications, an estimated 90,000-280,000 vaccinations were given to pregnant women, and 5,600-17,000 of those vaccinations were primary.

- Netherlands, 1959-1963: 15,000 vaccinated, Bern strain; no VIG administered; one fetal vaccinia case. Risk: 1:15,000.

- Netherlands, 1964-1970: 21,000 vaccinated, Elstree strain; VIG administered; no fetal vaccinia cases. Risk: 0:21,000.

VIG Prophylactic Experience. Sussman and Grossman (*J Peds*, 1965) did a review of VIG given for treatment or prophylaxis in 336 patients. It was dispensed from July 1960 through December 1963 by the American Red Cross after consultation with nationally recognized consultants. Of the cases with enough information available for evaluation, 239 reported vaccinia complications, of which 24 received prophylaxis. No adverse outcomes were reported for ten eczema patients who were given VIG. Generalized vaccinia was reported for one vaccinee who developed chickenpox after vaccination and another patient with hypogammaglobulinemia.

In Australia from 1960 –1975, the VIG dose used depended on whether it was given for therapy or for prophylaxis, and according to age. The doses ranged from 4 to 20 ml in the pre-standardized era; the concentration is now 500 IU/ml. Adverse events were analyzed for several risk factors: eczema, pregnancy, immunosuppressive therapy, prior reaction to vaccination, skin disease (other than eczema), malignancy, age <1 year, and miscellaneous factors. Two adverse events were reported: one “poor response” in a vaccinee with eczema and one death in a patient

with a malignancy. These occurred in a program that administered an estimated 4 million doses of vaccine over the 15 year period. Persons with active and quiescent eczema were vaccinated.

Sharp and Fletcher (*Lancet*, 1973) analyzed the data on 22 pregnant women vaccinated during the same period. Of these, 18 were deliberate vaccinations, two were accidental exposures to health care workers, and two were contacts of a vaccinee. Three spontaneous abortions occurred, all in three women who were vaccinated in their first trimester. They all received VIG within 24 hours of vaccination, but two aborted within 1 week of vaccination and one aborted 5 weeks after vaccination. No virologic studies were done on fetus or placenta. The data on the trimester of vaccination and VIG administration were not reported for the other women.

Discussion included question of what the risk of anaphylaxis from IVIG is in anyone, pregnant or not, since the rate of IgA deficiency in the general population is at least one in 750 people. Dr. Goldstein thought that those data might be available, but this also happens quite infrequently. The NIDF has advised not to give immune globulin to those pregnant.

Hyperimmune Globulin Prophylactic Use Among the Severely Immunodeficient

Dr. Lisa Rotz, formerly of NCID and now with CDC's Bioterrorism Program, reported difficulty in determining the size of the immunocompromised population. There are no overall estimates on the number of individuals with congenital or acquired immune deficiency. But, if broken down into some of the conditions known to be associated with immune suppression, it would include at least 900,000 people with HIV/AIDS, 8 million with some form of cancer, and ~184,000 organ transplantation patients undergoing immunosuppressive therapy. Additional groups at high risk of complications from smallpox vaccination include those with lymphoma or leukemia. About 91,700 such diagnoses were indicated in 2002 data.

The main responses expected from vaccination are the appearance of neutralized antibodies at about day 10 in primary vaccinees and days 6-7 in those revaccinated, and a peak at about day 21 after vaccination. The antibody titers are usually higher in revaccinees. Viremia occurs, usually before the appearance of neutralizing antibodies. The studies of cell-mediated immune responses after vaccination indicate that delayed hypersensitivity after vaccination could occur around day 7 in primary vaccinees and earlier in revaccinees (Fulginiti VA, Kempe CH, et al, *Immun Defic Dis in Man,* 1968; 29).

The most serious complications associated with immune suppression occurring after vaccination, for which prophylactic VIG may be used to prevent, would be progressive vaccinia or vaccinia necrosum. These rare but very serious reactions have been reported in those with humoral or cell-mediated immune deficiencies. The latter has the poorest prognosis. There is no clear cutoff for the level of immune suppression required for the development of this complication, and the outcome has generally been fatal before the advent of VIG therapy.

Dr. Rotz outlined the theoretical benefit of prophylactic use of VIG, to explain the general immune defects associated with the development of progressive vaccinia and why VIG was effective in some but not others (Fenner, et al; *Smallpox and its eradication*. 1988, WHO; p.161, adapted from Fenner, 1972). Potential immune system defects include:

- Cell mediated immunity with intact humoral system (thymic dysplasia), in which progressive vaccinia develops and is not improved with VIG.

- Intact cell mediated immunity with impaired humoral system (Bruton's agammaglobulinemia), in which a normal response to vaccination can occur, or progressive vaccinia can develop because of a possible "overwhelming" of cell mediated immunity. VIG restores that and helps decrease the antigenic load.

- No cell mediated immunity and no humoral system (the Swiss syndrome), in which progressive vaccinia develops and is not improved with VIG.

- Acquired immune deficiencies, where one or both of the arms of the immune system are depressed but were not congenitally absent. As in Bruton's concept, if progressive vaccinia develops, it is probably due to an overwhelming of the cell mediated immunity. VIG could supplement the cell mediated immunity functioning to a level where it can ultimately control the infection.

The bottom line is that cell mediated immunity function is probably needed to ultimately recover from progressive vaccinia, but what level is needed remains unknown.

VIG as treatment of progressive vaccinia. Of 24 cases reported in the English language literature from 1966-present, relevant to the use of VIG and development of progressive vaccinia, underlying conditions cited were: chronic lymphocytic leukemia (6), lymphosarcoma (3), combined immunodeficiency/undefined B/T cell defect (6), hypo-IgG or delayed neutralizing Ab (3), Hodgkin's Disease (1), leukemia (1), and four were unknown.

The therapy reported was VIG alone; VIG and other therapy; methisazone; transfer factor or exchange transfusion from recently re-immunized individuals, or interferon; no treatment, and unknown treatment. Ten of the cases resolved (4 CLL, 2 lymphosarcoma, 1 hypo-IgG, 1 leukemia, 2 unknown) and 14 died. Other data/studies on treatment have shown better responses with reported overall decrease in mortality to 20% or lower.

Three case series were done on immunocompromised individuals (either that from therapy or accompanying such conditions)

3. Sussman and Grossman (*J Peds*, 1963) studied 356 VIG releases from July 1960-December 31, 1963 to 336 patients. They reported on VIG effects for 239 treatments and 24 prophylactic administrations after diagnosis by a referring physician. In the immunocompromised group, all three who received prophylactic VIG had hypogammaglobulinemia and one developed generalized vaccinia. One patient with leukemia also received VIG but there were no data on response. The authors concluded that VIG was effective as a prophylactic
1. Sharp and Fletcher (*Lancet ,*1973) studied VIG releases in the U.K. between 1967-1971. Of 661 responses to their survey (~50% return rate), 65% reported prophylactic VIG use. Of the reports, 407 were deliberate vaccinations and 13 were accidental; 11 were contacts with contraindications. About 80% given VIG on the same day as vaccination, the rest ~14-18 days later. Of the 5 on immune suppressive treatment who received VIG given for

"complications after vaccination", two did not develop further complications, one developed benign generalized vaccinia, one a severe local reaction, and one died from progressive vaccinia. Of the two leukemia patients "accidentally" vaccinated, one had a severe local reaction requiring skin grafts before healing, and one developed encephalopathy 3 months later and died. The authors felt that prophylactic VIG was effective, but the discussion supporting that relied on data from eczema and pregnancy groups.

2. Ferry (*Vox Sang* 1976) conducted a survey of 1685 questionnaires (870 prophylaxis, 815 treatment) over a 15 year period when 4,900,000 doses of smallpox vaccine were distributed (the amount administered was unknown). VIG was used prophylactically because of contra-indication, history of previous adverse reaction, or desire to attenuate vaccine response because of systemic disease, debility, or convenience because of impending travel. Those on immunosuppressive therapy were 18.8% of the prophylaxis group, and most not on a true immunosuppressive dose. But six patients were on immune suppressive doses of medicines and had normal vaccine site reactions. Among the 2.5% with malignancy, one myeloid leukemia patient died of progressive vaccinia; the responses of three were unknown. With most evidence based on eczema vaccinatum, the authors concluded that VIG was effective in prophylaxis. Although they could not conclude that prophylaxing those with malignant disease was without risk, they felt that VIG should be given at time of vaccination to decrease the risks.

The limitations of these case series studies lay in case ascertainment and data collection, that the level of immune suppression was not documented, and that the incidence of uncomplicated vaccination among immune compromised individuals is unknown.

The data on *HIV and live vaccines* include:

- One case report of generalized vaccinia, and possibly progressive vaccinia, in a vaccinated military recruit who had a CD4 count of <25 and opportunistic infections at presentation. Treated with weekly VIG for 12 weeks, his lesions resolved but his CD4 count also rose over this period to 300.
- Three deaths were reported following the development of "injection site necrosis" in individuals (all with CD4 counts <50) receiving vaccination with a recombinant inactivated vaccinia HIV vaccine. One vaccine antigen was identified at the site of necrosis in one patient, and one had herpes virus hominis superinfection.
- Five others receiving compassionate use of this vaccine had no problems (no CD4 count), nor did 14 other patients who were regular study participants. CD4 count of ≤300 was required for enrollment. Case reports of disseminated infections (measles and BCG) associated with other live pathogen vaccinations are also in the literature.

Dr. Rotz' conclusion was that control of vaccinia infection and healing of the vaccination site requires some function of cell-mediated immunity. This is indicated by the poor response to VIG by those with no cell mediated immunity function and that those treated with chemotherapy (which attacks cell immune system response) prevents a normal vaccine reaction/response; and reports of resolution of progressive vaccinia in instances where cell mediated immunity is somewhat restored as seen by restoration of delayed hypersensitivity reaction among those who had none when presenting with progressive vaccinia. But the level of cell mediated immunity

required remains unknown, since variable response to VIG was seen in patients (e.g., for those with CLL, it was dependent on the disease activity).

So, if the CMI function is required to recover from progressive vaccinia, then theoretically, prophylactic VIG would not be expected to prevent this complication if a severe CMI defect is the problem. This defect would not be expected to correct itself or improve. Conversely, if the benefit of VIG is its help to restore an overwhelmed CMI when the normal humoral antibody response is absent or delayed, then prophylactic VIG might be expected to prevent progressive vaccinia in situations where the normal antibody response would be expected to be delayed or absent.

VIG may prevent or attenuate adverse events such as progressive or generalized vaccinia, due to an overwhelming or prolonged viremia from a delayed neutralizing antibody response. This is suggested in that progressive vaccinia due to humoral immune defects with functioning CMI should theoretically respond to VIG treatment, and progressive vaccinia response to VIG in conditions where the CMI is "overwhelmed" but restored when VIG is given (i.e., delayed-type hypersensitivity response absent initially but present following VIG).

Finally, Dr. Rotz posed two questions to the ACIP

1. Based on existing data, does prophylactic VIG have a proven benefit for preventing progressive vaccinia?
2. If the data are insufficient to support proven benefit for this complication, does the theoretical benefit of VIG strongly support its consideration in certain situations?

Discussion included:

- There are few data to answer #1, but #2 makes theoretical sense. If there is no fetal vaccinia seen in the 170,000 doses of the NYBOH strain given in 1947, and there is some comparable detectable risk from anaphylaxis due to IVIG, there must be some risk benefit ratio. The women in 1947 probably had already been vaccinated, but even for those not exposed to vaccine, Dr. Offit suspected that the benefits of VIG probably outweighed its risk.

- Activation of complementary anaphylactoid reactions and anaphylaxis were concerns, but VIG is given at a lower dose, and traditionally immunoglobulin products can be delivered in pregnancy. If the VIG available is intramuscular, not an IV product, it could be used. And IgA deficiency can be tested and reported overnight. However, the VIG under discussion is an IV product.

- This raised some of the questions about beginning any therapy in pregnancy that might challenge the immune system and risk aborting the fetus, although in this case the risk of vaccinia probably would be higher. Dr. Gall reported that Rh-immune globulin is given to all pregnant women who are Rh-negative at 28 or 30 weeks. Antiphospholipid syndrome seems to be increasing, and IVIG is used to treat that. He had not personally seen any such reaction, but immune globulin given IM or IV has been described. While some fetal vaccinia has been reported in the literature, it is exceedingly rare. If a pregnant woman was inadvertently immunized for smallpox, he expected that treatment with something like RhoGAM would be sufficient.

- *Was the theoretical risk of VIG due to mercury in the old product?* Dr. Goldstein recalled that it was assigned category C due to lack of study in pregnant women. Dr. Midthun added that none of the immune globulins such as RhoGAM contain thimerosal any longer.

- *Lack of data pertains to varicella zoster and IG. What is the comparability of VIG with VZ?* Dr. Modlin said there are individual risks in pregnancy, though not high, in using immune globulin among pregnant women. But here, although the risk is very small, the risk of IG could outweigh that of fetal vaccinia. And, there is also the unknown issue of efficacy. Dr. Gall stated that varicella given within 96 hours of exposure ameliorates varicella disease, and is well tolerated.

- So the question was whether to alter the current use of VIG under an IND, and whether to add prophylactic use as an indication for the IND, in these two situations (immunocompromised or pregnant). It is unlikely that a woman would discover within five days of vaccination that she is pregnant, but for civilian use, CDC would like to be prepared.

- The IND could be modified so that VIG could be offered, but doing so under an IND requires definition of the circumstances under which this would be appropriate.

- Dr. Modlin summarized the ACIP's consensus that it would be reasonable to offer VIG, without using the word "recommend".

Pediarix™ PRESENTATION

Dr. Tejprapat Tiwari, of the NIP, introduced the presentation of SmithKline Beecham Biological's (SKB) new DTaP-Hep B-IPV combination vaccine, Pediarix™. It was licensed by the U.S. FDA on Dec 13, 2002 and is a pentavalent formulation to provide protection against five diseases: diphtheria, tetanus, pertussis, hepatitis B, and poliomyelitis. The DT, TT and pertussis components are equivalent to Infanrix™; the hepatitis B surface antigen (HBsAg) is equivalent to Engerix™, both SKB vaccines; and the poliovirus is equivalent to Aventis Pasteur's IPV.

Safety/Immunogenicity

Dr. Barbara Howe, of SKB Biologicals, presented the data from the clinical safety and immunogenicity data for Pediarix™, (TM) licensure in U.S. in 1997 and outlined their future research plans. The current harmonized schedule requires 20 vaccinations to fully immunize infants to age two years. Combination vaccines offer advantages to children (fewer injections), clinicians (better acceptance, simplified storage/administration and staff freed for other medical activities); and the community (lower overall costs and higher compliance, leading to more effective vaccination programs).

Pediarix™ has nine product components: D, T, PT, FHA, PRN, HBsAg, and polio 1, 2, and 3. The history of Pediarix™ components and the antigenic composition of each was provided:

- The DTaP component is the same as Infanrix™ which was licensed in 1994 and in the U.S. in 1997. About 62 million doses have been distributed world wide, and 95 million as DTaP alone or in six combination products.

- The hepatitis B component is the same as Engerix™-B, licensed in1986 and in 1989 in the U.S. Now licensed in 145 countries, >735 million doses have been distributed world wide.
- The IPV component is an enhanced potency, inactivated trivalent polio virus vaccine similar to Aventis' U.S.-licensed IPV, using the same manufacturing process, strains and antigen content. SKB's IPV has been in clinical development since 1989. It was tested in 78 trials among ~25,000 children, either as IPV alone or in combination. It was first licensed in 1996 in France in combination with DTaP; since then, 17 million IPV dose equivalents have been distributed world wide in four combination products.

The indication sought for Pediarix™, licensure was for active immunization against diphtheria, tetanus, pertussis, hepatitis B and poliovirus types 1, 2 and 3, as a 3-dose primary series in infants born to HBsAg negative mothers, beginning as early as 6 weeks of age. It is also permitted after the birth dose of Hep B vaccine. Booster doses with recommended vaccines (e.g., Infanrix™ and Hib in the second year of life) are still required.

The basis for licensure was, according the FDA CBER's guidance, a demonstrated non-inferiority of this combination for safety and efficacy, compared to U.S.-licensed vaccines. Studies were conducted in ten different countries, involving 7028 infants and >20,000 doses of Pediarix™. The studies conducted in Germany and the U.S. were presented, as they included a separate injection comparative group to allow the non-inferiority evaluation.

Immunogenicity Study 015: data compared to separately delivered vaccinations:
Study design (Yeh et al, *Pediatr Infect Dis J*, 2001; 20:973). 400 infants were equally randomized in two groups; one received Pediarix™ co-administered with IPV/OPV or IPV and the second received separate injections at 2, 4, and 6 months of age. (OPV was standard of care at the time of the study).

- Seroprotection for diphtheria, tetanus, and HBsAg were demonstrated as equivalent and GMT was numerically higher for Pediarix™ than the separately administered vaccines.

- The three pertussis components, PT, FHA and PRN, demonstrated high ≥91% response rates and, again, the GMTs were numerically higher.

- OPV: The proportion of detectable antibody indicated a 99% seroprotection. GMTs for polio 1 and 2 were higher in those who received OPV and for polio 3, higher in those who received Pediarix™.

- IPV: again, seroprotection was 99-100%, but GMTs were higher for polio 1, 2, and 3 following Pediarix™.

- Non-inferiority testing for *seroprotection and vaccine response* rates was calculated in absolute numbers, subtracting the Pediarix™ group from the separate injection group for each antigen. Within the 95% CI, all the antigens except FHA had upper limit of the pre-specified limit for 10%. The FHA upper limit was at 12.5% Non-inferiority measured by GMTs was calculated by dividing those of the separately delivered antigen by the combined vaccine. All three pertussis antigens, including FHA, were in the 90% CI within the pre-specified limit of 1.5

- The Pediarix™ response was that co-administered with Hib was also compared to separate injections and showed comparable results in GMT levels.

Study 015 Conclusion: Pediarix™ is least as immunogenic as separately administered vaccines including OPV; at least as immunogenic as IPV with respect to response rates to polio 1, 2, and 3; and showed no negative impact on co-administered Hib vaccine.

Study 011: Safety Compared to Separately Administered Vaccines:
Design. This German study (Zepp et al, *Pediatrics* 2002; 109:e58) was originally designed as a four-arm study, in which all arms received Pediarix™ co-administered with one of four different manufacturers' Hib vaccines (groups 1-4). Another group receiving separate vaccines plus OPV (group 5) was added. Vaccines were give at a 3, 4, and 5 month schedules. The objective was to compare Pediarix™ to separately-administered U.S.-licensed vaccines to determine the proportion of subjects reporting at least one solicited symptom rated as "grade 3" (clinically relevant and interrupting normal daily routine). Non-inferiority would be demonstrated if the upper limit of the 90% CI for the difference between pooled Pediarix™ groups and the control group was below the pre-specified clinical limit of 7.5%. The number of vaccine antigens was unbalanced in this study, which is most likely to bias the analysis in favor of the control group (fewer antigens for Hep B)

The proportion reporting any grade 3 symptom was 16.2 for Pediarix™ and 20.3 for those receiving separate injections. The upper limit of the difference between the two was 1.41, which met the primary objective.

Local reactions. Local reactions measured were represented on bar charts. The Pediarix™ group's response was comparable to that of the Infanrix™ group for incidence of pain by dose, and did not seem to increase with successive doses. The same was true for redness and for swelling by dose, although it increased between doses 1and 2 for both groups, but not for dose 3.

Solicited general symptoms were for diarrhea, loss of appetite, restlessness, and vomiting, all of which were reported in similar rates. However, those receiving separate administrations had statistically higher rates of unusual crying, and there was a higher rate of fevers ≥103.2_ F in the Pediarix™ group. The grade 3 symptoms were all similar, except for restlessness.

Study 011 Conclusions. Pediarix™ was found to be at least as safe as separately administered U.S.-licensed vaccines with respect to the percentage of subjects with any "grade 3" solicited symptoms, or for unsolicited symptoms, as described above.

SKB explored the higher rates of fever >100.4F in the Pediarix™ and Hib recipients in both studies 011 and 015. Both groups had similar duration of fever, mostly lasting 1-2 days and 98.5% resolving during the 4-day follow up period. Antipyretic/antibiotic use was similar, as was follow-up on cases of sepsis and fevers within 7 days of vaccination. Hospitalization with any fever within 7 days post-vaccination was similar (0.23% for the Pediarix™ group and 0.39% for control vaccine recipients), as was the rate of discontinuation due to adverse effects. The higher incidence of low fever did not seem to result in any clinically relevant consequences.

Prevnar Co-Administration

Prevnar was not commercially available when the study was designed. However, a statistically significant increased rate of fever ≥100.4_F was observed when Prevnar was co-administered with the other "standard of care" vaccines (DTaP, Hep B, IPVC, Hib). So, SKB studied fever when Prevnar was co-administered with Pediarix™ to children on a 2, 4, 6 month schedule. Data analysis is ongoing, but the preliminary data indicate that, co-administered with Prevnar, Pediarix™ recipients showed no significant increase in fever >101.3_F (the primary endpoint). Only 1.2% of Pediarix™ recipients sought medical advice for fever. There was no potentiation of fever rate when Pediarix™ was co-administered with Hib and Prevnar. The differences in the fever rates were of the same magnitude as were previous studies when Prevnar was not co-administered.

Study 030: Safety Following the Birth Dose of Hepatitis B
Gylca et al *(Vaccine* 2001, 18:825) conducted Study 030 in Moldova, examining two vaccines given concurrently with the Hep B birth dose at 6, 10, and 14 weeks: DTaP-Hep B-IPV + Hib and DTaP-IPV/Hib + Hep B. The rates of local reactions (grade 3 pain, redness and swelling >20 mm) were slightly higher than systemic reactions for the three doses.

Study 003 Birth Dose 0-14 days. Pichichero et al (*Pediatr Infect Dis J*.2002; 21:854) studied the birth dose from 0-14 days in the U.S. among two groups: Pediarix™ administered alone and Pediarix™ given with Hep B. The schedule was 2, 4, 6 months. The percentage of subjects with any "grade 3" solicited symptoms was almost identical and well below the cutoff needed to demonstrate no inferiority. The *Study 003 conclusions* were that three doses of Pediarix™, with or without Hib, were well-tolerated after a dose of Hep B vaccine at or shortly after birth.

Serious Adverse Events were reported as studied in 12 clinical trials that included 182 subjects. Of those, 199 serious adverse events (SAE) were reported in 2.1% of Pediarix™ vaccinees and 1.8% of the comparison group. Eight SAEs were considered possibly or definitely related to the study vaccine: six fevers (one patient with a severe reaction at the Hib site and three with possible viral infections), one reaction at the Hib site with no fever, and one uticaria. Other SAEs explored were hypotonic hyporesponsiveness, encephalopathy, and anaphylaxis. None of the 7028 Pediarix™ vaccinees in 12 clinical trials reported any of those conditions.

Safety and Reactogenicity Conclusions
In these 12 clinical trials with active follow-up and standardized methods, the rates of both solicited and unsolicited adverse events were similar to those of separately-administered U.S.-licensed vaccines. A higher rate of fever was observed, but did not result in clinically relevant consequences. The vaccine was well-tolerated after a birth dose of Hep B, and the combination of antigens did not place infants at an increased risk of clinically relevant adverse events.

Dr. Howe presented a chart of the routine harmonized immunization schedule to demonstrate how Pediarix™ could reduce the number of injections scheduled for 1-6 months, from 14 injections to eight. She then outlined Pediarix™, market status for supply. High demand is expected, but GSK could accommodate almost double that forecasted. To ensure access to all children, Pediarix™ will be priced similarly to the separate component parts). Demand in the private sector has been very high since the product was launched on January 6 (>300,000 doses have been sold). Reimbursement policies across the U.S. cover 90% of all babies Pediarix™.

Discussion with Dr. Howe included:

- *What is the GMT after 4 hep B doses followed by three doses of Pediarix™, compared to the traditional monovalent three doses? And how does the vaccine cost compare?* The group without a Hep B birth dose had a GMT of 1240 and those who received it had a GMT of 2996. In general, the Pediarix™ GMT is higher than that cited in historical studies of different manufacturers' hepatitis B monovalent vaccines on a 0, 1, 6 schedule. Mr. Scott Howard, of GSK Vaccines, reported that the acquisition cost to private providers is about 4-5% above of the sum of the individual vaccines.

- *(Katz)Your firm has licensed in Europe a similar vaccine but also with Haemophilus influenza B. What is the likelihood of that coming to U.S. market?* Initially, Pediarix™ and Infanrix™ were licensed in parallel in a number of countries. Of the 25 countries involved, only 3, including the U.S., issued a commercial license. The reason is that the higher level combination was licensed at the same time, and the other countries chose to go with the higher level combination. GSK has discussed with FDA bringing the higher level combination to the U.S., but when that might happen is unknown.

- *Since type 2 polio is no longer found in the world, has GSK reconsidered having only types 1 and 3 in the IPV?* No. Dr. Modlin also noted that vaccine-derived type 2 polio was found in Madagascar.

- *If a provider began with Pediarix™ but then ran out of it, is there any difference in giving monovalent or another combination to complete the series?* The package insert has sections on beginning with individual components and then switching to Pediarix™ to finish the individual series, but there is no language on the reverse. It could perhaps be addressed in the interchangeability discussions.

- Dr. Offit expressed his thanks for the work to produce this vaccine and to reduce the required number of shots. He asked if there were any sense that this vaccine has caused a lessening of physician interest in giving the birth dose of Hep B? Dr. Howard, of GSK Vaccines responded that it is still early to know, but a telephone survey indicates 150,000 of the Pediarix™ doses sold so far have been used, with no impact so far on the birth dose. However, Dr. Wexler, of the Immunization Action Coalition, reported having received e-mails and phone calls from physicians and one organization asking if the birth dose is still necessary with Pediarix™.

ACIP Consideration of Pediarix™ Recommendation

Pediarix™ and an Accelerated Schedule

Dr. Tiwari continued with the Pediarix™ presentation. The vaccine is approved for the primary series of DTaP, hepatitis B, and IPV vaccination at 2, 4, and 6 months of age, preferably at 8 week intervals, but at least at 6 week intervals, among those aged from 6 weeks to 7 years. It may be used for catchup vaccination. It is not approved for booster doses after the primary series. Infants who receive the primary series of Pediarix™™ should be given a fourth and a fifth dose of DTaP (preferably as Infanrix™®) at 15–18 months and 4–6 years of age, respectively, and a fourth dose of inactivated poliovirus vaccine (IPV) at 4–6 years of age.

Whenever feasible, the same type of DTaP (i.e. Infanrix™) should be used for booster doses of DTaP after a primary series of Pediarix™.

Although Pediarix™ can be used on an accelerated schedule, this is complicated by the differences in the minimum ages and intervals for the different antigens. While the 6-week minimum age matches that recommended by FDA and ACIP for Pediarix™, as is DTaP and IPV, the minimum age for the third dose is determined by the hepatitis B vaccine component. A "valid" third dose of hepatitis B vaccine is recommended at 6 months (≥24 weeks), but DTaP and IPV given separately can be given as early as at age 14 weeks on an accelerated schedule. The minimum age for the second dose of Pediarix™ is determined by the minimum interval between the first and second dose, which is approved at 6 weeks. The ACIP approved use of DTaP and IPV at minimum intervals of 4 weeks after the first dose. There are no known data on the immune response to Pediarix™ if the second dose is given at a 4 week rather than 6 week interval.

The 2002 ACIP General Recommendations stated that sometimes, administering doses of a multidose vaccine at shorter than recommended intervals might be necessary. In those cases, ACIP accepted an accelerated schedule as long as it uses minimum intervals between doses that are recommended for routine vaccination. The minimum ACIP-approved intervals between the first and second doses of Hep B, DTaP, and IPV is 4 weeks.

Question to the ACIP: Would the ACIP recommend Pediarix™ at a minimum interval of 4 weeks between the first and second dose, when used on an accelerated schedule?
ACIP Response: Dr. Modlin saw no reason that should not be the case, to no objection.

Co-administration with other vaccines
Dr. Tiwari continued. If a provider uses Pediarix™ on an accelerated schedule, as might be done during an outbreak of pertussis, DTaP would normally be recommended rather than Pediarix™ to complete the third dose of DTaP. But, if Pediarix™ is given for the third dose on an accelerated schedule, the provider would need to give an additional dose of hepatitis B vaccine at 6 months (or ≥24 weeks of age) for optimal boosting.

In the case of Haemophilus influenzae type *b* (Hib) conjugate vaccine, Pediarix™ can be co-administered, since the Hib is administered with a separate syringe at a different injection site. It has a similar safety profile and an acceptable immunogenicity profile. Pediarix™ can also be co-administered with Hib and pneumococcal conjugate vaccines since they are given at separate injection sites and because infants are scheduled to receive other components of Pediarix™™. However, the higher rates of fever ≥100.4_F after dose 1 of Pediarix™ administered with both Hib and PCV7, compared to separately administered components, have prompted those data to be reevaluated after the safety trial.

Interchangeability of vaccines from different manufacturers
In 1999, ACIP stated that, in general, "...vaccines from different manufacturers that protect against the same disease may be administered interchangeably in sequential doses in the immunization series for an individual patient." In the case of DTaP vaccine, all doses of the vaccination series should follow the initial brand used. But, if it is not available, any DTaP

vaccine should be used to complete the series. It should not be deferred because the brand previously used is not available or is unknown.

Pediarix™ can be used interchangeably with the IPV or hepatitis B vaccines of other manufacturers if the child is also scheduled to receive the other components of the vaccine and if the other components are not contraindicated. And, since Pediarix™ has the same DTaP as Infanrix™, it can be used interchangeably for the primary DTaP series. And, although the safety and immunogenicity data are limited for the "mix and match" sequences of the DTaP series, Pediarix™ can be used interchangeably with other types of DTaP for that series if the initial DTaP used is unavailable or unknown. There are now several different DTaP vaccines with different antigenic content available, such as Acel-Immune®; Tripedia™®, and Daptacel™®.

Discussion included:

- The issue is interchangeability when there is a new product. Because DTaP vaccines differ in antigen and quantity, one cannot expect clinicians to continue to order separate vaccine plus Pediarix™.
- Dr. Baker supported a comment about the minimum interval for the accelerated schedule, and asked for data on Pediarix™ relative to that. Dr. Howe reported Pediarix™ as tested on several accelerated schedules, such as studies of 3, 4, and 5-month schedules done outside the U.S. For the hepatitis B component, the seroprotection rate proportionally with 10 million IU/ml three studies was ≥97%; the GMT was lower, as might be expected (~750-800).

Pediarix™ and HBsAg Status

Dr. Anthony Fiore, of NCID's Viral Hepatitis Division, presented the data on the Pediarix™ and hepatitis B vaccination series to infants born to HBsAg antigen positive mothers or mothers with unknown HBsAg status.

The Hep B coverage data gathered b the National Immunization Survey from 1992-2000 among 19-35 month-olds reflected steady progress, to 90% who had received ≥3 doses. But coverage decreased by 1% (40,000 fewer children vaccinated) for the first time in 2001. Greater flexibility in the schedules may encourage vaccination to return to a positive direction.

The VFC recommendations will have to change with the advent of Pediarix™. In planning for that, four aspects of how Pediarix™ would likely be used were kept in mind by the NIP: 1) ACIP's preference for the birth dose of hepatitis B; 2) its preference for combination vaccines; 3) its acceptance of a 4-dose hepatitis B vaccine series when combination vaccines are used; and 4) the idea that consistent but flexible recommendations are desirable regarding use of combination vaccines for all infants.

A revision for the Hep B VFC statement was crafted, which parallels that drafted for the combination Hep B/Hib vaccine Comvax™. The recommendation accepted Comvax™'s use in all infants to complete the hepatitis B series (2, 4, 12-15 months) after the birth dose, regardless of maternal HBsAg status. That provided an example of acceptable 3- and 4-dose schedules using combination vaccines. So, the draft VFC statement allows Pediarix™ and Comvax™ to be used whenever administration of any of the components are indicated ***and*** if other components are not contraindicated.

Three infant hepatitis B vaccination tables were presented to the committee, each with several alternative schedules using single antigen and combination vaccines for infants according to the mother's HBsAg status.

Immunogenicity/safety data. FDA has previously approved a 4 dose schedule (Engerix™-B: 0, 1, 2, 12 months) for use in all infants. Comparison of Pediarix™-Hib (2, 4, 6) with or without Engerix™-B at birth demonstrated that all the of infants in both groups had seroprotective levels of anti-HBs at completion. Higher GMCs were seem for the Engerix™-B/Pediarix™ (4 dose) group, but the safety data were similar.

Even if providers switch to Pediarix™, many infants will still receive the hepatitis B birth dose, followed (as it can be already with Comvax™) by the 3 dose Pediarix™ series, resulting in a 4-dose hepatitis B vaccine series. With the licensure of more combination vaccines, the 4-dose hepatitis B vaccine schedules will likely become more common. ACIP has already heard the relevant immunogenicity and safety data, and ACIP and FDA have already approved a 4-dose schedule for infants, using the single antigen Engerix™-B vaccine. The safety and immunogenicity comparison data for a 4-dose, single antigen and Pediarix™ combination had just been provided at this meeting, demonstrating at least equal immunogenicity and no increase in adverse events.

So, beginning the hepatitis B vaccine series at birth with a single antigen vaccine and then completing the series with a combination vaccine series satisfies established ACIP preferences, preserves the "safety net" function of the birth dose, and offers the advantage of fewer injections than with single antigen vaccines.

HBsA+ or Unknown HBs status mothers. The Pediarix™ package insert indication is for infants born to HBsAg-negative women, similar to the Comvax™ insert. Both vaccines cannot be given before 6 weeks, and the recommended first dose is at 2 months. Pediarix™ contains the same antigen formulation as in Engerix™-B, which has established efficacy and safety among infants born to HBsAg+ women, and their response to Pediarix™ parallels that to Engerix™-B, regardless of maternal HBsAg status. That includes the proportion who develop seroprotection, the GMT, and the adverse events profile.

In light of that, CDC believes that it is reasonable to conclude that effective post exposure prophylaxis is provided when a dose at birth of single antigen vaccine and Hepatitis B immune globulin (HBIG) is followed by a 3 dose Pediarix™ series beginning at 8 weeks. In 1997, the ACIP discussed similar issues when Comvax™ was accepted for use in all infants regardless of maternal HBsAg status. The draft VFC statement now presented to the ACIP allows for use of both Comvax™ and Pediarix™ for all infants.

Efficacy of Immunoprophylaxis among Infants Born to HBsAg+ and HBsAg- Mothers by the Time of Second Dose. One issue with using combination vaccines for infants at high risk of perinatal infection is the fact that these vaccines cannot be given before 6 weeks of age. A study was described which involved infants born to HBsAg+ mothers and therefore at the highest risk of infection, who appropriately received a birth vaccine dose and HBIG. The data indicate that giving the second dose at 2 months still provides effective immunoprophylaxis. The unpublished

data of two studies (C. Stevens et al) was shared, in one of which children received 0.25 mcg of antigen at 0, 2, 6 or 0, 2, 4, 15, and the other received 0.5 mcg at 0, 1, 6 or 0, 1, 2, 12. Very few infants in either group developed chronic infection, and the efficacy was the same. Dr. Fiore pointed out that the dose used in the group receiving dose 2 at 2 months was half the currently licensed dose.

In another study (SA Marion et al, *Am J Epidemiol*, 1994), perinatal hepatitis B prevention was evaluated retrospectively, with vaccination on a 0, 1, 6 schedule and HBIG at birth. There was little difference between the serological outcome of the regular schedule and that of a small subset who received dose 2 at ≥2 months.

Hepatitis B immune globulin (HBIG) and/or hepatitis B vaccine provides substantial protection against perinatal HBV. Two studies have demonstrated an HBIG efficacy of 42% (dose at birth, no vaccine) among infants born to HBsAg+ women who were recommended to also receive HBV (Beasley *J Infect Dis*, 1983), and that 8-30% of infants develop protective levels of anti-HBs by 1 month after first HBV dose (Andre, Am J Med 1989).

So, based on these data, the provision of the vaccine at birth is of primary importance in preventing perinatal HBV infection, not whether the second dose is given at 1 month or 2 months, and providing the second dose at 2 months does not change the effectiveness of post exposure prophylaxis with vaccine.

Since 1993, the CDC-funded Perinatal Hepatitis B Prevention Program has provided case management for HBsAg+ pregnant women and their infants to ensure proper immunoprophylaxis and post vaccination testing. This provides a mechanism with which to monitor trends in hepatitis B vaccine coverage in infants at high risk of perinatal infection, as well as the effectiveness of post exposure prophylaxis.

Dr. Fiore summarized that Pediarix™ may be used in a Hepatitis B vaccination series for any infant because:

- Immunogenicity and safety are established when combined with a hepatitis B vaccine dose at birth.
- When combined with hepatitis B vaccination at birth, Pediarix™ is expected to have high efficacy in prevention of perinatal HBV infection.
- The combination gives providers consistent and flexible vaccination schedule recommendations.
- Mechanisms are in place to monitor effectiveness.
- This may encourage higher hepatitis B vaccine coverage and series completion on schedule.

The great success of the birth dose against hepatitis B to reduce hepatitis B virus infection among children is now being seen. For example, a routine infant/childhood vaccination program begun in 1990 included an emphasis on providing the first dose of vaccine at birth. In 11 years, this achieved a dramatic drop in perinatal and early childhood infection. Rates plummeted from 1.6% for chronic (i.e., HBsAg+) infection and 4.5% for serologic evidence of previous infection, to only 0.4% (one

child) and 0.2% (5 children), , respectively. Similar examples have been seen in children in Alaska and children in Georgia born to Asian immigrants.

Dr. Fiore summarized that routine vaccination during infancy works and vaccination beginning at birth is a big part of why it works. Combination vaccines fit well into the strategy to eliminate HBV transmission and they should be combined with routine hepatitis B vaccination at birth.

The apparent anticipation of combination vaccines' release was reflected in the 2003 harmonized schedule, which stated a preference for receiving the first dose of Hep B vaccine soon after birth; using only monovalent Hep B vaccine for the birth dose; that all infants should receive the first dose of Hep B vaccine soon after birth and before hospital discharge, but that the first dose may also be given by age 2; that monovalents or combination vaccine may be used to complete the series; and that four doses of vaccine may be given when a birth dose is given.

The *proposed VFC resolution* stated that Pediarix™ is an acceptable hepatitis B vaccination option for infants at 2, 4, and 6 months, regardless of the mother's hepatitis B surface-antigen status, including those infants who have received a dose of hepatitis B vaccine soon after birth. *ACIP Response:* Dr. Modlin asked if the 2, 4, 6 month schedule after the birth dose was felt to be adequate, to general **agreement**.

Discussion included

- *The text "including the birth dose" infers that one could wait to give the infant, born to a surface antigen positive mother, the first hepatitis B immunization until 2 months.* That wording will be changed. **The committee agreed to the questions.**

- Dr. Midthun reiterated that the indication is for infants born to antigen-negative mothers. There are no data that compare this product's usefulness in infants born to HBsAg positive mothers who then are vaccinated against Hep B at 0, 1, 6 months versus those who receive a birth dose and the subsequent routine follow-up, nor are there data on the impact on efficacy from waiting to 2 months, which is why FDA provided a narrow indication. And, while there are safety data on children receiving Pediarix™ at 2, 4, and 6 months as well as a birth dose, those data are limited (100 children). The work has not been done to indicate that all infants can routinely be given four doses with Pediarix™ given after the birth dose. Finally, while it is true that FDA had approved Engerix™ B for 0, 1, 2, 12 months, that was only for infants and older individuals needing accelerated protection from hepatitis B.

- The AAP received many calls about this, so an AAP News and notice on its Web site followed the package insert. For simplicity, they could backtrack on this, but the ACIP should be aware that the package insert was already cited.

- *Is there any problem with insurance issues on this (e.g., an extra dose)?* Dr. Zink, of GSK, stated that most often, the birth vaccinations are considered part of the prepaid maternal hospitalization benefit for mother and child, and most insurance companies HMOs will not micromanage that. Since it is already included in that capitation, the policy for managed care actually favors a birth dose. The three subsequent doses have been covered by 90% of insured children, and he expected that 100% would be so by the end of the quarter.

- Dr. Wexler noted that Pediarix™ was said to only be used for the primary series, but the ACIP General Recommendations say it can be used as indicated if there is not contraindication. She suggested that the ACIP consider relaxing the primary series to allow the use of Pediarix™ for a 15 month-old or even a 5 year-old who had not had the third Hep B vaccination.

- Dr. Richard Judelson was a CDC EIS Officer and is now doing public health and private practice in the center city of Buffalo, NY. He was disturbed by the NIS reflection of 95% coverage for single antigens such as DTaP among 2 year-olds, but a decline to 75% for full immunization. In some regard, those gaps are created in the provider community's confusion, among their busy schedules, to find space for new vaccines, and among parents about multiple antigens and vaccines. The answer is combination vaccines, and VFC is an important component of their successful utilization in clinic settings, where most antigens have to be delivered in the fewest number of visits (given proper timing intervals), and in private offices, where most of the VFC immunization is done. Clinicians in either settings do not want a dual system, but rather uniformity of private and VFC patients. Swift ACIP approval will go a long way toward implementation.

Programmatic Issues Related to Pediarix™

Dr. Lance Rodewald, of the NIP, summarized the programmatic issues related to combination vaccines. The obvious good is fewer injections for full protection, decreased resource needs (injection time and equipment) and, possibly, fewer missed opportunities.

However, there are challenges. For public health, those include measuring coverage (registries, hand held records, ensuring the NIS records it all accurately), ensuring that the hepatitis B birth dose happens, making the combination vaccine VISs user-friendly, and adding to the vaccine stockpile and managing it. And for clinicians, there will be more types of vaccines to stock in their refrigerators and issues related to the administration fee. That is generally linked to the number of injections, so fewer of those bring less revenue. The administration fee supports the private clinician's immunization services, a topic that is well described in the February *AAP News.* Combination vaccines are a great example of how biotechnology is helping clinicians to help children. The challenges are surmountable; they just need proper attention.

Discussion included:

- *It is wonderful that this combination vaccine is coming available. But is there any thought given to parent choice (e.g. to prefer individual vaccines)?* Dr. Modlin felt that this would be a matter of what vaccines are available. While the universal purchase states may offer more choices, many other locations, and certainly private physician offices, may not. Dr. Orenstein added, though, that many public health programs allow physician choice, but those that choose at the state level will likely make a single choice.
- Dr. Jackson noted the high private sector demand already evident and suspected that this was an indication of the satisfaction of the physician or parent at getting this rather than monovalent. Dr. Howard agreed, thinking that the public and private reception will parallel, and added that many practitioners are probably waiting on the ACIP's decision, since they may also use VFC.

VFC RESOLUTIONS

Dr. Wharton commented, as noted by Dr. Rodewald, the complexity posed to incorporating this combination vaccine into the Vaccines for Children (VFC) program, to be consistent both

internally and with previous formats; even though it does offer an opportunity to decrease immunizations at the 2, 4, and 6 month visits.

She offered three VFC resolutions, that were based on several assumptions. These were that the ACIP agrees: 1) with the proposal to make the vaccine available through the VFC to infants born to hepatitis B surface antigen-positive women; 2) to accept the minimum intervals presented; and 3) that the vaccine is recommended for use in the primary series, as indicated in the package insert. There is no provisions for booster doses in the second year of life.

Combined Resolution for Vaccines to Prevent Polio
"Pediarix™ can be used for the first, second, and third dose of IPV, if the other vaccine components of the combination are not contraindicated." This is consistent with previous language on combination vaccine. The contraindications of DTaP to the IPV statement (page 2 and 3) were also added.

ACIP response: No questions.

DTaP Resolution changes added, under "Eligible Groups", the qualifiers on the ages for which Pediarix™ is approved (corrected on page 2) to be similar to the polio statement regarding doses1-2-3, and noted that the components are not indicated.

Dosage Intervals. The minimum interval for Pediarix™ of 6 weeks for doses 1 to 2 and of 6 weeks for doses 2 to 3 was changed, based on this meeting's discussion, to 4 weeks for the DTaP series, acknowledging that this poses a potential problem for hepatitis B. She asked if this was the ACIP desire. This was a difficult question. The committee had said yes before, but now was focusing specifically on the hepatitis B interval.

Discussion included:

- The hepatitis B statement has a similar table in which the interval between doses 2 and 3 was set at 8 weeks. But it was felt important that the table be clear that the third dose should not be given at <6 months. The present footnote on that is bolded in the current version and can be retained.

- The critical element is to have a reasonable interval between dose 2 and 3 for most recipients. The hepatitis B schedule already has a minimum interval of 4 weeks between doses 1 and 2. In the past, 4 weeks was not thought to be an adequate interval; the minimum has been 2 months. Changing that would also change the ACIP's General Recommendations, developed with much hard work over a long period of time.

- Dr. Orenstein felt that the hepatitis B interval between doses 2 and 3 should be longer, and that inserting a DTaP interval there would be misleading. The intervals should be consistent with polio for this vaccine, DTaP and for hepatitis B. If hepatitis B is the driving force, he advocated for putting in the hepatitis B footnote and explaining why it is longer than elsewhere.

- However, when Dr. Wharton sought confirmation that the minimum interval for dose 2 to 3 should be 8 weeks, Dr. Margolis, of the NIP, noted that this only pertains to an accelerated schedule. An accelerated schedule for DTaP will clearly affect the ultimate performance of

hepatitis B vaccine among young children. The accelerated DTaP in a child <6 months of age will not involve the same point immunogenicity for hepatitis B. Dr. Modlin agreed that it should remain for those reasons.

- Dr. Wharton read the footnote, stating that the last dose of hepatitis B vaccine should be given at ≥24 weeks of age with an interval of 8 weeks after the second dose. Dr. Orenstein framed the issue as whether this should be used in an accelerated 4-week schedule if one is immunizing against hepatitis B at the same time. He reiterated that the hepatitis B interval should be retained and footnoted as to why it is different. Dr. Modlin summarized the committee's agreement that the minimum interval for hepatitis B in an accelerated schedule should be 8 weeks, with a footnote noting the minimum interval from dose 2 to 3.

- Dr. Margolis commented that, from a practical standpoint, an accelerated vaccination may prevent the use of this vaccine. A monovalent DTaP would have to be used. And if there is a pertussis outbreak, it could probably not be used while also keeping to the hepatitis B needs for primary immunization.

- When Dr. Wharton asked if the committee wished to express its preference to not to use this vaccine on an accelerated schedule for prevention of pertussis, Dr. Modlin thought there to be no choice in the matter.

- Dr. Howe related that, in the study where hepatitis B vaccine was given at birth followed by a 6, 10, 14-week schedule, the GMT for hepatitis B was ~1000, in the setting of having a birth dose of hepatitis B and then following with the combination given on an accelerated schedule. Dr. Modlin appreciated that, but found it not completely germane to this discussion. An infant receiving an accelerated schedule most likely has not received a birth dose, impelling the ACIP's great caution.

Dr. Wharton added one minor editorial change on page 4 that struck a reference to "one combination" since there are now more than one, and the reference to pregnancy related to Pediarix™, given that it is not recommended for the age group in which that should be an issue.

The ***final hepatitis B resolution changes*** were summarized for the committee's vote:

- Pediarix™ was added to the eligible groups on page 2, with two vaccination schedule options. In Option #1, a single antigen is used at birth, 8, 16 weeks and 6 months of age; or, Option #2 Pediarix™ is used at 8 and 16 weeks and 6 months.

- Two vaccination schedule options are included for Pediarix™: Option #1, a single antigen hepatitis B vaccine is used first, followed by doses in which Pediarix™ could be used between 8 weeks and 6 months of age; and without a birth dose, Option #2, in which doses are given at 8 weeks, 16 weeks and 6 months, the recommended schedule.

- Language about permissive use of the combination when any component is indicated for the primary series if no components are contraindicated. The third dose should be given at least 16 weeks after dose one, but not before 24 weeks of age. Dr. Wharton was unsure that this was consistent with the minimum intervals just added to the other resolution.

- A schedule for infants born to HBsAg+ mothers which includes a birth dose of single antigen vaccine. This vaccine can be used use at 6-8 weeks of age, with a second dose at 16 weeks of age and a third dose at 6 months. The language was similar to that one page 2.

- A similar schedule to infants born to mothers with unknown status for hepatitis B surface antigen was added on page 4.

- The catch-up schedules are listed in this statement, but there is no reference made to this vaccine in the proposed resolution.

- Regarding the minimum age and dosage interval table schedule, Dr. Wharton noted that these statements do not present the information in a way that is uniform between resolutions. This table indicates a minimum age of 6 weeks; a minimum interval of 4 weeks from dose one to two (consistent with the DTaP statement); a minimum interval of 8 weeks from dose 2 to 3 (the change made on the DTaP statement); and a minimum interval from dose 1 to dose 3 of 16 weeks with a footnote specifying to not vaccinate infants aged <24 weeks. Contraindications cite the age restriction for availability of Pediarix™; the DTaP contraindications were added; and the reference to pregnancy was dropped on the assumption that it would not pertain to this vaccine. (It was an IPV contraindication).

Dr. Zimmerman moved to accept the three VFC resolutions as modified, and was seconded by Dr. Tompkins.

Dr. Modlin noted that he and Drs. Levin, Offit and Rennels were not eligible to vote, due to a conflict with the manufacturer *or any manufacturer of the components*. That left only seven eligible members, not a quorum. Dr. Snider deputized the ex-officio members to vote if they so wished, specifying that they must to state any conflicts if they did vote. None stated a conflict.

Vote
In favor: Zimmerman, Word, Tompkins, Birkhead, Brooks, Hanson, Salamone, Graydon, Evans
Opposed: None
Abstained: Rennels, Offit, Levin, Modlin, Midthun, Heilman and Gellin

The resolution passed.

With no further comment, the committee adjourned at 6:20 p.m. and reconvened on the following morning at 8:30 a.m.

FEBRUARY 27, 2003

AGENCY UPDATES

Department of Defense
Dr. Diniega reported on the DOD vaccination program, which has vaccinated 250,000 personnel for smallpox. Since the anthrax vaccine program resumed last fall, 750,000 personnel have been vaccinated since 1998. Adenovirus continues to be a problem at training centers and vaccine

supplies were depleted in 1999. A contract with the vaccine manufacturer was signed in 2002 and will take 4-5 years to delivery of the product. All new recruits are to be vaccinated against hepatitis B. Sera have been taken after vaccination to test for antibody to HBsAg, and showed 30% overall to be seropositive (39% female, 28% male). All services will screened before vaccination.

Reported adverse effects from smallpox vaccination include 1% who developed a macular papular flat rash. This is a benign presentation, but multiple providers have concluded that it was generalized vaccinia, leading to isolation and other unwarranted responses. DOD is conducting more education on distinguishing between rash and generalized vaccinia.

Discussion with Drs. Diniega and Grabenstein included:

- The rash appeared in both primary immunizations and revaccinees.

- *What is defined as generalized vaccinia? In the past, it was assumed that generalized vaccinia did contain vaccinia virus. And, NIP's photo of generalized vaccinia on an arm and wrist with pox looks like smallpox; do any of them look that bad?* PCR and culture are used to retrieve vaccinia virus from pustule rashes with widespread distribution, but that has not yet been seen. Most cases resolve quickly, with pustules present for a day or two and then gone, so they are clearly not generalized vaccinia, and they are relatively diffusely spread, rather than being a rash or pustules. Dr. Modlin reported that the Smallpox Workgroup is also struggling with defining generalized vaccinia. Clear photos will help the field to a proper diagnosis.

- Pathology is being done on some of these rashes (e.g., one was biopsied from Kuwait), but the results were not yet in.

- NIH had seen these rashes and found them to be not generalized vaccinia. The pathology shows a folliculitis, similar to enhanced acne, that the smallpox vaccine seems to have evoked. Dr. Grabenstein agreed that there is a folliculitis group, but that is not in the group that DOD is calling generalized vaccinia at the moment.

Food and Drug Administration

Dr. Midthun reported FDA's December 2002 licensure of the Pediarix™ combination vaccine of DTaP, hepatitis B and IPV, by SmithKline Beecham. IPV is a new component not previously licensed in this country. The vaccine's schedule is at 2, 4, and 6 month of age. The immune response is comparable to individual vaccines, with the most common reactions being fever and fussiness. Fever occurred more frequently after administration of Pediarix™,™ compared with separately administered vaccines.

Other new approvals included a supplement: to Wyeth's smallpox vaccine for a 100-dose kit with a new diluent and needles, and another to Aventis Pasteur's DT pediatric vaccine for a trace-thimerosal formulation. In December 2002, VRBPAC discussed a license application for FluMist, for influenza prevention in healthy persons aged 5-64 years in three age groups: 5-17, 18-49 and 50-64 years. The majority of members voted that the safety data are adequate for those three age groups. VRBPAC met again in February and voted to retain the

A/Caledonia/20/99 and B/Hong Kong/330/01 strains. They postponed the A (H3N2) selection until March.

National Institutes of Health
Dr. Heilman commented on the new federal project, Bioshield's, component of rapid vaccine development. Two RPA vaccine contracts have been awarded for rapid development of a recombinant protective antigen for anthrax, and the other for a modified vaccinia Ankara as an replacement or adjunct to the current vaccine. Next on the agenda is accelerated development of a plague vaccine. NIH also recently catalogued B and C agents to identify missing knowledge requiring research. She offered copies of the Jordan report for further information on NIH's vaccine development research.

Clinical trials. Vaccines in current trials include 13 malaria vaccines and 16 more TB vaccines ready to enter clinical trials. Regarding the outbreak discussed on the previous morning, all agencies are coordinating with the NVPO to implement a pandemic influenza plan. NIH has Dr. Rob Webster in Hong Kong to conduct surveillance and he is sending samples to develop seed strains for the H5N1 strain. NIH is also partnering with industry to respond to a pandemic influenza outbreak and to provide reagents for WHO. The FY04 research plan focuses on safety, working with FDA to develop tools for the detection of adventitious agents, which are hoped to help FDA make licensure decisions.
Work is ongoing with GSK on an Phase III efficacy trial for HSV and an ACIP workgroup to address this would be helpful. Nonhuman primate trials are still going on to study thimerosal issues, focused on ethyl- versus methyl mercury in vaccines. A study in Argentina on thimerosal-containing vaccines is also being done.

National Vaccine Program Office
Influenza Preparedness. Dr. Gellin reported on NVPO's progress in developing the pandemic influenza preparedness plan. They have begun to develop a response plan to the Hong Kong outbreak situation. Two DHHS staffers are working internationally: Dr. Keiji Fukuda in China and Dr. Lorna Simonsen at WHO in Geneva. One hundred million dollars of the FY04 budget was budgeted for pandemic preparedness, working with industry to develop a year-round influenza vaccine production capacity for a pandemic. A robust production base is needed for surge capacity.

Administrative. He reported that Dr. Eve Slater had stepped down as Assistant Secretary of Health. USPHS Vice Admiral and Surgeon General Richard H. Carmona, MD, MPH, FACS, took her place.

Vaccine Supply. The NVAC's Vaccine Supply Workshop report was posted on the NVPO Web site and the proceedings will be in *Clinical Infectious Diseases* later this year. The Workgroup on Vaccine Supply issues remains active. A resolution was passed encouraging CDC to develop best practices for registries.

Polio eradication: NVAC will serve as the U.S.'s national certifying organization in the global polio eradication program. This was decided in response to a request from Dr. Walter Dowdle, who is leading the U.S. laboratory poliovirus containment component, and who reported to the committee.

Smallpox. A joint workgroup is looking at the issues related to smallpox vaccine, including future vaccine candidates. Some manufacturer presentations were heard, and clinical trials will be reported as they occur.

Influenza preparedness accompanies bioterrorism preparedness, and a Workgroup on Global Preparedness was formed a year ago. Last year, a Task Force on Pandemic Influenza met in Mexico to discuss the barriers to vaccine development and to some of the antiviral issues that perhaps could be accelerated by this group. Canadian work on biosecurity issues also includes pandemic influenza.

Dr. Peter added discussion by NVAC on the proposal to develop an OPV stockpile, including issues of how much to stockpile. An ACIP/NVAC workgroup was formed to address this.

Dr. Birkhead reported that the state and local levels are much more prepared now for an influenza pandemic than they were 6-12 months ago. Smallpox preparedness helped the states' preparedness to deal with the NPS, create local vaccination sites, etc. Compared to smallpox, the pandemic influenza issues seem much more manageable. Dr. Gellin added that communication will be the key element and could be a model for subsequent events.

Vaccine Injury Compensation Program

Dr. Geoff Evans reported on the VICP's latest claim and compensation statistics.

- Claims filed: 814 for FY03, accomplished in only 4 months, a significant increase over the total of 956 for FY02. The increase is related to thimerosal-related injury claims.
- 447 hepatitis B claims, 10 for Hib, 20 for VZV, 30 for RV, 5 for PCV, and 100 for DTaP.
- Claims adjudicated: five pre-1988 claims remain. The average time for adjudication of post-88 claims is 3 years.
- $1.4 billion has been awarded, and $1.8 billion remains in the trust fund.

Thimerosal litigation. A new trend in civil litigation began in 2001. There are currently >200 claims filed against vaccine manufacturers and vaccine administrators. They involve different types of lawsuits: traditional tort claims alleging that a specific child was injured and seeking lifetime care; a "medical monitoring" class action suit, in which individuals without current neurologic injury are asking for periodic checkups to detect potential future problems; and derivative" claims by parent, legal guardians or spouses (e.g., for loss of companionship).

The National Compensation for Vaccine Injuries Act (NCVIA) requires petitioners to file first with the VICP, but these claimants argue that thimerosal is an "adulterant" or "contaminant", not covered by the NCVIA, so they are not suing for "vaccine-related" injuries. The NCVIA also excludes medical monitoring claims of <$1000. DHHS and DOJ issued a "Statement of Interest" asserting that the claims should go first to the VICP, and most decisions on the "adulterant" issue have agreed with that stance. But decisions have differed regarding other civil actions. These lawsuits have been called the greatest threat to future vaccine supply by an industry representative at Senate Committee Hearing in September 2002.

A parallel trend of increases in VICP litigation began in FY02. Of nearly 2000 claims filed, 75% were related to thimerosal injury. An Omnibus Autism Proceeding issued Autism General Order #1, which consolidated the cases of claims alleging autism or developmental disorders caused by thimerosal-containing vaccines or MMR vaccine. A two-year schedule was adopted for discovery, evidentiary hearings and a decision. The conclusions reached will apply to individual cases. Unique short-form petitions are being filed with little or no medical records required. Petitioners can opt-in or -out of the omnibus autism proceeding, or leave to seek remedies in tort system. By law, the Special Master must reach a decision within 240 days of the claim. The time is just about up for some of these cases now.

The Homeland Security Act of 2002 was passed on November 25, 2002, and contained some of Sen. Frist's VICP bill provisions regarding thimerosal. The Act defined vaccine-related injury or death; added a definition of "vaccine" and clarified the definition of "manufacturer". The latter extended coverage of the Act to manufacturers of thimerosal, and applies to all pending civil actions. On February 20, these provisions were removed and signed by the President. Dr. Evans drew particular attention to one provision; the law includes provisions stating Congress's intent to introduce a bill to "ensure that patients who have suffered vaccine-related injuries have the opportunity to seek fair and timely redress, and that vaccine manufacturers of components or ingredients of vaccines, and physicians and other administrators of vaccines, have adequate protection, not later than 6 months after the date of enactment of this Act."

National Center for Infectious Diseases

Dr. Alison Mawle, of the NCID, reported the success of pneumococcal conjugate vaccine in Alaska, presenting unpublished data from CDC's Arctic Investigations Program. It showed a

dramatic reduction of invasive pneumoniae in Alaskan native children. A statewide program, operating since January 2001, made pneumococcal conjugate vaccine available. Coverage rates by October 2002 were 70% for 3-15 month-olds and 39% in 16-29 month-olds. The cases dropped from 350 per 100,000 in 1999-2000 to ~100 in 2002. There is an indication of herd immunity, as cases dropped to 33% from 83% in children aged <2 year and 20% from 76% in children aged 2-17. An effect in adults has not yet been seen, nor has any effect from the shortages.

National Immunization Program

Dr. Orenstein reported record lows for measles, mumps, rubella, and tetanus. But pertussis posted the largest number of cases since the mid-1960s, much due to adolescent/adult transmission. ACIP was asked to consider whether an adolescent/adult booster for pertussis may be needed.

The President's proposal on improving childhood vaccine programs to fund and help accomplish ACIP recommendations includes:

1. Improvement of vaccine access by the under-insured. The need for this was demonstrated by pneumococcal conjugate vaccine which, when not covered by VFC, led to a two-tiered policy to administer it only to those VFC-eligible. The President's proposal would open up the VFC's benefits to children with insurance that does not include immunization ("under insured") if they seek care at public health clinics. To avoid making this a disincentive to manufacturers, these children would be folded in to the VFC coverage. No anticipated change in the public/private market share would result. This is only designed to take the pressure off 317 vaccine purchases and to improve VFC access to the under-insured by using state and local public health clinics. This would take the pressure off 317 vaccine purchases and state funds to cover immunizations, at an estimated net cost of $40 million.
1. The restoration of Td and DT to the VFC program, which had been dropped and price-capped, respectively. This provides an incentive for manufacturers to bid on the contract at an estimated cost of $10 million. MMR is currently the only vaccine selling at the capped price; the others sell below cap.
2. Improve the six-month national stockpile of childhood vaccines, financed through VFC, by 2006. From FY2003-FY 2006, $707 million would be spent, as would $172 million in FY03.

The President's FY04 budget request for discretionary immunization is $518 million, a decline of $110 million from FY03, all taken from the Section 317 Grant program. It also includes $1 million for pay raises, but takes $1 million out for "personnel rightsizing" and IT reduction. The budget request for the VFC program increased by $87 million over FY03, to $1.063 billion; and $81 million for is budgeted for program operations, a $2 million increase.

Discussion with Dr. Orenstein included:

- *The problem is that under-insured children will only be vaccinated if they go to public health clinics. In some ways, that is a step backwards; children should be going to a medical home.* Agreed, but there will still be a big 317 budget left over. The point of this was to solve the problem of under-insured children without changing market share, and to fold a lot of them into the entitlement. The real goal is to eliminate under insurance, something the IOM report to be issued this summer will address. But there should not be many more children at public clinics because they already are covered by the 317 program.

- *Will the $11 million going to measles flow through the Red Cross program?* How that will be spent is unclear, but it is in partnership with the ARC.

- Dr. Schaffner urged NIP to include, in future vaccine reports, varicella, hepatitis B and hepatitis A, pneumococcal disease and influenza, and to delineate national immunization between children and adults.

- Dr. Tom Vernon, of Merck Vaccines, thought the problem not to be that children are under- or uninsured. He encouraged the AAP and others to look into first-dollar insurance coverage for children. He also suggested adding, to the definition of under-insured, the inclusion of co-pays for children who are covered. Dr. Orenstein responded that NIP's definition is those without insurance for immunization coverage, but not those with large deductibles.

EVIDENCE-BASED TABLES IN ACIP RECOMMENDATIONS

Drs. Kathy Neuzil and Schaffner offered comments on the use of evidence-based tables when issuing ACIP recommendations. Relative to the work that that would involve, Dr. Modlin noted the 7 present ACIP workgroups and a potential of forming as many as 5 more, and asked if the committee wished to discuss this further. Dr. Snider reported CDC's anticipation that ACIP membership would soon be up to the full complement of 15 members.

Dr. Neuzil summarized ACIP's Policy and Procedures document of October 2002, which asked for citation of the strength and quality of the evidence supporting each major recommendation, and a summary score for evidence and strength of recommendation. Currently, ACIP guidelines have been developed by an evidence-based approach, recognizing the differences in strengths of evidence between recommendations. *MMWR*'s publication on specific vaccines includes detailed reports with comprehensive documentation and extensive references.

She and Dr. Schaffner suggested that ACIP develop a uniform rating system to make the recommendation easier to interpret by the clinicians or organizations who implement it. The text of the *MMWR* published recommendation is not amenable to quick reading, and the tables often do not convey the evidence basis for the recommendation. If that is not a standard procedure, the ACIP's strongest recommendations could be undermined by appearing to be equally weighted to the weaker ones.

To communicate the rationale behind recommendations, the U.S. Preventive Services Task Force has recommended the development a uniform rating system that transparently and explicitly links the recommendation's strength to the quality of evidence. This ensures that the review of evidence is comprehensive, objective and attentive to quality. She and Dr. Schaffner proposed forming an ACIP workgroup to discuss the best way to communicate the quality of data behind the vaccine recommendations and the nature and strength of the recommendation.

Discussion included:

- Dr. Snider commented that ACIP policies and procedures reference an internal CDC document that gives guidance on how to provide guidelines. One part of that is the evidence approach recommended to CDC, which is also used by HICPAC and the joint NIH/CDC group that discussed opportunistic infections. It would be good for ACIP to move in this direction to

improve the utility and credibility of its guidelines. Some concerns have been expressed that ACIP has to address some issues without much data and base their recommendation on expert opinion, but the workgroup should at least explore this issue. Evidence-based recommendations are becoming the standard approach and not using it risks a loss of ACIP leadership.

- That approach was begun that with the pneumococcal statement, which cited the strength of the evidence. A workgroup is advisable, but the amount of work required will require staffing. The AHRQ supports the USPSTF; perhaps CDC could do this internally.

IOM IMMUNIZATION SAFETY REVIEW COMMITTEE UPDATE

Dr. Kathleen Stratton updated the ACIP on two reports, the fourth and fifth of the IOM Immunization Safety Committee's eight scheduled reports. Their past reports to date have addressed the reputed association between:

- *MMR and autism.* Findings: rejected causality; mechanisms are "fragmentary".
- *Thimerosal and neurological disorders.* Findings: inadequate data for causality assessment; mechanisms are "plausible".
- *Multiple immunizations and immune dysfunction.* Findings:
  -- Risk of Infection: rejected causality, but mechanisms are strong.
  – Risk of autoimmune disease (IDDM): rejected causality and mechanisms are weak.
  – Risk of allergic disease (asthma): inadequate for causality and mechanisms are weak.

On this day, Dr. Stratton reported on the committee's safety review of the biological plausibility of an association between the administration of hepatitis B vaccine and neurological disorders, and on the SV40 contamination of polio vaccine.

Hepatitis B Vaccine and CNS/PNS Neurological Disorders were chosen for examination since these are serious neurological disorders and known clinical entities. Links to hepatitis B vaccine have been questioned regarding CNS disorders such as MS (onset or relapse), ADEM, optic neuritis and transverse myelitis, and regarding peripheral nerve disorders such as GBS and brachial neuritis. Published epidemiological studies and case reports have investigated those associations with Hep B vaccines. There is also a substantial body of literature on the pathophysiology of several of these conditions.

The committee did not examine the putative association between Hep B and infant death, nor any possible role of hepatitis B vaccine in relation to undefined conditions with a neurological component that would be of concern to adults who are now ill.

Multiple Sclerosis. The evidence base regarding hepatitis B and MS is limited but very well done. The Nurses Health Study published data on incident MS (nested case-control study, RR of .6), and two unpublished studies offered consistent findings of no association between hepatitis B and incident MS. There was only one published study from Europe on relapsing MS, which was a case-crossover study. She described the committee's work:

- *Causality* was explored for Hep B vaccine administered to adults and both incident and relapsing MS. The literature on the first episode of CDD, ADEM, optic neuritis, transverse myelitis, GBS and brachial neuritis was not strong and the evidence was inadequate to accept or reject a causal relationship.

- *Biological Mechanisms*: The theoretical basis and indirect biological evidence of a link was found under contrived experimental conditions in rodents, in whom immunization leads to a demyelinating disease similar in many respects to MS, ADEM, or GBS. A causal relationship also was found between several other vaccines and ADEM, GBS, and brachial neuritis. However, the evidence is tangential and animal models have not provided evidence that HBsAg serves as a trigger for the onset of demyelinating disease. Infection with HBV is not proven to cause MS or GBS and no vaccine has been causally associated with MS. The biological evidence is not clearly and directly relevant to the hepatitis B surface antigen in the vaccine and there is no evidence that HBsAg is: 1) capable of bystander activation of a Th1-type response; 2) a superantigen or a molecular mimic with a myelin-related antigen; or 3) an inducer of nonspecific polyclonal activation.
  Conclusion. The committee concluded that the evidence was weak for biological mechanisms by which hepatitis B vaccination could possibly influence an individual's risk of the central or peripheral nervous system disorders.

- A *significance assessment* was done of the disease burden associated with multiple sclerosis, including physical disabilities, high cost of care, and economic effect on employment (e.g., loss of income and access to health insurance). Also examined were the safety concerns in France, prevention strategies related to hepatitis B infection, acceptance of hepatitis B vaccine in the U.S., and the need for understandable informational material.

- *Surveillance recommendations* included: 1) continued surveillance of MS and other CNS and peripheral demyelinating disorders, especially in health care workers and those born since 1991; 2) development of case definitions and guidance for the diagnostic evaluation of the demyelinating disorders that are reviewed to improve vaccine adverse effects surveillance and, when appropriate, causality assessment; and 3) continued surveillance of hepatitis B disease and increase surveillance of secondary disease such as cirrhosis and hepatocellular carcinoma. The latter will serve to ease skepticism about the birth dose by demonstrating decreases in the effects of a hepatitis B infection

- *Basic/clinical research recommendations* were to continue research in animal and *in vitro* models, as well as in humans, on the mechanisms of immune-mediated neurologic disease possibly associated with exposure to vaccines.

SV 40 Contamination of Polio Vaccines

A potential 10-30% of the 100 million doses of IPV (primarily) that were distributed from 1955-1963 were contaminated with SV40.

- *Causality.* A good evidence base was available for review: seven studies of cancer incidence, three of mortality, and two controlled trials of prenatal exposure to SV40 through vaccination of the infants' mothers. However, the studies' limitations were that they were mostly of an ecologic design; there is potential bias from misclassification of those who might have received the contaminated vaccine; and that the rarity of the potentially resulting tumors frustrates study.

Conclusion: Therefore, although many (but not all) studies were negative, the committee found the evidence inadequate to accept or reject a causal relationship between SV40-containing polio vaccines and cancer. This was a controversial decision; some thought that the committee was too conservative. But its response was that this process relies not on numbers but on the quality of the evidence, similar to what was just discussed regarding the evidence basis of recommendations .

- *Biological Mechanisms*. The committee explored whether SV40 can cause cancer in humans under conditions of natural exposure. The data base is growing, although the results are somewhat inconsistent. Multi-lab studies of the detection of SV40 are somewhat conflicting and detection in tumors does not by itself demonstrate a causal relationship. *Conclusion.* The committee concluded that the biological evidence is moderate that SV40 exposure could lead to cancer in humans under natural conditions.

- More biological mechanisms were explored, such as whether contamination of polio virus vaccine with SV40 is associated with SV40 infection in humans. There are other possible sources of exposure, and there is some evidence of exposure before 1955. However, exposure to IPV from 1955-63 cannot be equated with exposure to live SV40 or to infection with SV40.

  Conclusion: The biological evidence is moderate that SV40 exposure from the polio vaccine is related to SV40 infection in humans.

When reported at the last NVAC meeting, one member asked how, if there is debate about the studies, the evidence could be "moderate". The answer was that moving from theoretical to weak evidence requires a low floor, but quite a bit is needed to constitute strong evidence. This was in the middle. The question was whether the committee could in future articulate better how the evidence moves from moderate to strong. In part, this is a factor of the iterative manner in which this committee proceeds. They tried to be clear, but the criteria not as clear as all would like.

- *Significance assessment.* The committee found concerns about exposure to SV40 through inadvertent contamination of polio vaccines to be significant, because of the seriousness of cancers as the possible adverse health outcomes and because of the continuing need to ensure and protect public trust in the nation's immunization program
- *Policy review.* The committee found no need for a policy review, since the current vaccine is free of SV40. But it did recommend a policy analysis of the vaccine contamination prevention and response plan. This should identify procedures already in place or those that need to be developed; include strategies for routine assessment of possible vaccine contamination; notification of public health officials, health care providers, and the public if contamination occurs; identification of recipients of contaminated vaccine; and surveillance/research to assess health outcomes associated with the contamination. Among the factors to consider is a program to store samples from each vaccine lot approved for release and development of better mechanisms to identify the recipients of vaccine from specific lots (e.g., registries).
- *Research recommendations* included development of sensitive/specific serologic tests for SV40 and development and use of sensitive/specific standardized techniques for SV40 detection. Once there is agreement in the science and protocols, pre-1955 samples of

human tissues should be assayed for the presence or absence of SV40 in rigorous multi-center studies. Further study of the transmissibility of SV40 in humans was recommended, but until some of the technical issues are resolved, the committee did not recommend additional epidemiologic studies of people potentially exposed to the contaminated polio vaccine.

The next report to be issued will address sudden unexpected death in infancy. The next IOM Immunization Safety Committee meeting will be held on March 13, 2003, and will address influenza vaccine and neurological disorders. This will be Web cast in audio at www.nationalacademies.org, and, as possible, the slides used will be archived later.

Discussion with Dr. Stratton included:

- *There has been some concern about who reads the reports, how they are understood and how they are disseminated and utilized. This last report does not distinguish well between SV40 and polio vaccine containing SV40. This is not applicable to people who were not vaccinated 40 years ago.* That confusion was not brought to the IOM's attention, and media reports were consistent about the report. The committee thought that the separation of the causality assessment regarding vaccine and that of biological mechanisms from other sources was clear; but if not, it could try to do a better job. Regarding dissemination, she had informally polled people attending last year's immunization conference. It seemed that many read summaries and abstracts , but the SV40 report received little attention from the field. Whether that was due lack of interest or some other reason remains unknown.

- *How are the committee's topics chosen?* The Interagency Vaccine Group chooses them, and the NVAC Safety Subcommittee discusses and recommends topics to the NVAC, which then recommends to the IAVG. Dr. Evans described the process.

- *The research recommendations on SV40 were also the conclusion of an interagency open meeting on SV40 held about 5 years earlier and sponsored by the NVPO, and there was substantial difference of opinion between the labs of different PHS agencies. Who will take the responsibility to answer the question of who will read the committee's document and follow how the agencies implement those recommendations?* Dr. Gellin responded that the safety issue context is part of the broader reach he hoped to bring to his position at NVPO.

- Dr. Peter added that the IOM contract has a three-year term.. Recommendations for continuation will be discussed by NVAC, but the decision is the government's. CDC also is evaluating the significance of the findings and their usefulness.

VACCINE STORAGE AND COLD CHAIN ERRORS

Dr. Greg Wallace, of the NIP, reported concern expressed by state health departments, project directors, and vaccine providers over the lack of specific guidelines for appropriate responses to vaccines stored at improper temperatures.

Cold chain errors are costly. A recently published study of >700 primary care providers (*Am J Prev Med* 2002;23(4):246-253) indicated that 17% had refrigerators that fell out of appropriate temperature range and 89% of the refrigerators that were out of range were <2^{o}C during the last 30 days. Seventy percent of those were <0^{o} C. Based on those data, an estimated 10.0% -

11.2% of provider vaccine refrigerators are below freezing temperatures at some point during a 30-day period.

If that is applied to CDC vaccine purchases for CY 2000, NIP estimated that 4.8 to 5.3 million doses were invalid, presenting an estimated vaccine loss cost between $57 million to $64 million. If 2°C is used as a cutoff, that could rise to $91 million. In addition, the $57-64 million only considers the cost and excise tax for VFC-funded vaccine (~50-55% of national purchase). It does not include the cost of recall/revaccination campaigns or non-monetary costs such as public confidence in immunization in general and their relationship with their provider in particular. A recent meeting of the WHO and UNICEF discussed the problem of freezing due to cold chain errors, which involves examination of the impact of freezing on vaccines and the extent of the problem to arrive at options for prevention and strategies for global anti-freeze action.

Options. *Choosing a refrigerator.* Dr. Wallace offered several options for ACIP's consideration. For guidance on choosing a new refrigerator, these could be: 1) no new recommendations (CDC currently suggests using a household- or commercial-style refrigerator/freezer unit with the refrigerator and freezer having separate doors); 2) recommending that providers evaluate the performance of their vaccine storage units and replace them if necessary (guidelines are needed); 3) recommending a timed phase-in of completely separate refrigerator and freezer units that meet quality specifications; or 4) other guidance.

Guidance on *temperature monitoring* could be: 1) No new recommendations (CDC currently suggests using one of three types of thermometers – Biosafe Liquid/Max-Min/Continuous); 2) formalizing recommendations on thermometer specifications/certification, placement, and documentation; or 3) issuing a new recommendation for use of temperature indicators; or 4) other guidance.

As discussed at the October ACIP meeting, public health's response to cold-chair errors has been to endorse revaccination as the most practical response to ensure protection from vaccine preventable diseases. Providers and health departments are concerned about cold chain issues, and some consideration has been given for serology testing. Serology is needed to verify protective antibody levels, but this involves very complex issues, and has not been addressed by the WHO. With certain exceptions, serology testing cannot have a major role in responses to cold-chain errors.

Discussion with Dr. Wallace included:

- The last time this was discussed, ACIP favored a focus on education rather than on serology. The preference of the group, regarding choosing a refrigerator, was that providers evaluate the performance of their vaccine storage units and replace them if necessary, but guidelines are needed for this.

- The VFC's practical approach to these issues is accomplished through the program's site visits, but for policy, they also rely on recommendations. Both the CDC and state health departments issue videos on vaccine storage/handling. There is a clear need for unified federal communication and guidelines.

- In the last ACIP discussion of this, the committee decided not to go beyond vaccinating children who might have been affected by cold chain failure. But now, a little more specificity is needed, particularly to address the issues of public trust in light of potential mass vaccination.

- *Perhaps CDC's guidelines could be made more specific, for example, to provide state- to state guidelines.* Each state creates its own materials for VFC providers, individually, and these tend to be general (e.g., ensure temperatures from 2°-8° C and monitor that). CDC also provides but does not stress the same message, it, as well as to only keep lots for a certain number of years and to check the refrigerator/freezer twice a day or to buy a new one. However, some providers may not be able to or want to absorb such costs.

- Dr. Wexler reported the states' desire for some uniform guidance in national standards, based on CDC recommendations.

- These data are sobering; clearly there is no assurance that a good enough system is in place. Dr. Birkhead supported recommending Option B as a minimum. He would also recommend that separate units be used, since storage in the refrigerator compartment too close to the freezer is a big part of the problem.

- Dr. Zimmerman, who works in the inner city, commented that the last thing anyone wants to do is to give impotent vaccine to these children. But installing a new refrigerator is probably not in the clinic budget, nor is the need for a carpenter to build the space for it, etc. This would not be a trivial expense. If a provider's system is not broken, he felt, there is no need to fix it; simply providing more detail is sufficient. Then, if providers' evaluation shows that they cannot safely store vaccines, they will take steps.

- Having to document the temperature check will help, but even good documentation does not ensure that the problem is taken care of until after it has been documented many times. Many health departments are now double-checking those to make sure that does not occur in another adjunctive preventive measure, but the tracking capacities are not equal across states.

- Development and implementation of a QC program would be helpful.

- There was general agreement to select Option B, incorporating the temperature recommendations as well, and for NIP to publish that as a supplemental recommendation in the *MMWR*.

SHOTS 2003 PDA SOFTWARE

Dr. Rick Zimmerman outlined and demonstrated the Shots 2003 PDA software, which is designed to assist in maintaining children's immunization schedule. It now also includes the adult schedule. This is freeware that runs on both color and non-color palm pilots or pocket PCs. There were over 30,000 downloads in 2002 and 10,000 to date this year, and to rave reviews. He demonstrated the software, which is based on ACIP recommendations and includes a reference to VAERS. Updates depend on the version used, but each has an expiration date, or posts a warning in February of the following year. Reminder emails are not sent out, but annual updates as the schedules change are planned.

VACCINE SUPPLY UPDATE

Mr. Dean Mason updated the committee on the status of the nation's vaccine supply. It has stabilized and is now sufficient for national demand for almost all vaccines.

Td vaccine rebounded to pre-shortage levels. There is no CDC contract for Td, but legislation has been proposed to remove the price cap on it, which would now allow VFC to purchase it. The price from Aventis and Schein/GIV/Caligo is $10/dose. Massachusetts Biologic Laboratories is still producing limited quantities of Td. The outlook is good; a return to the full dosing schedule was published in *MMWR* on June 21, 2002, including recalls, boosters, and the school entry dose.

DTaP: The annual national use of DTaP is 20 million doses. In CY01, 18.7 million doses were delivered, and 20.3 in CY02. CDC's contract need is about 60% of the national supply. In the 13-months from January 2001 to January 2002, only 49% of supply went through the CDC contract, but 61% did so in February to December 2002. The DTaP supply outlook was improved by Pediarix™'s licensure for 3 doses in the primary series through age 6 years, along with Daptacel™'s licensure on May 14. The price per dose for these, Infanrix™ and Tripedia™ ranges from $11.75 - $12.75. A return to the full dosing schedule was published on July 12, 2002. A CDC contract with GSK for Pediarix™ probably will be signed in the next two weeks, following the ACIP's recommendation.

MMR: The annual national need for MMR is 12-13 million doses; CDC contracts for 60% of the supply. In CY 2001, 11.7 million doses were supplied, as were 12.5 million in CY02. However, between October 2001 and February 2002, the average monthly supply was only 735,000 doses, or 73% of the national need. But the current outlook is good, with no backorders >15 days in the system. A return to the full schedule was published July 12, 2002.

Varicella: The annual varicella vaccine need is 6-7 million doses or 550,000/month. Over 6 million doses were supplied in each of the last three years. However, the same issues affecting the MMR supply affected varicella, with an average of 210,000 doses/month released from November to January, 2002 representing a 65% decline from the previous 10-month average. A significant increase began in April 2002, and the current outlook is good with no backorders. Return to the routine schedule was announced on August 2, 2002, allowing full dosing, recall, and re-institution of day care, Head Start and school attendance requirements.

Pneumococcal Conjugate vaccine. The supply of PCV-7 in CY01 was 15.5 million doses shipped and 11.4 million doses in CY02, with 52% and 53% respectively going through CDC. About 71% of national need was supplied in CY02. Beginning in July 2001, significant month-to-month variance occurred that lasted to the present, frustrating a return to the full dosing schedule. CDC's estimated national need was met only 4 times in CY02 and 11 times in CY01. Almost no vaccine was supplied in May, July and December 2002, and the >2.5 million doses supplied in November were <15% of national need.

However, a good supply in January 2003 led to reduced backorders (~400,000 doses), and the manufacturer indicates a supply sufficient to return to the routine schedule next month. The outlook is for a sufficient supply by May to meet the national need each month, and perhaps sufficient to return to the routine schedule in second quarter 2003. The reasons for the PCV-7

shortages and delays included rapid implementation in the public sector, demand exceeding the manufacturer's projections, GMP issues, and production interruptions.

Hib: Wyeth, which had 30% of the national market share, temporarily dropped manufacturer of Hib vaccine. The estimated national need annually for all Hib containing vaccine (Hib, DTAP/Hib and Hep B/Hib) is 18 million doses, 54% going through the CDC contract. Aventis and Merck to date have been able to supply Hib vaccine in sufficient quantity to make up for Wyeth's shortages. The two keys to the Hib vaccine supply's stability have been Aventis and Merck's negotiation of an adequate supply with CDC and the expected resumption of manufacturer by Wyeth by the third quarter 2003.

Other vaccines: Meningococcal vaccine by Aventis Pasteur is in sufficient supply, as are Hep A and B; Merck is taking 4-6 weeks to fill Hib orders, but hopes to normalize their supply by late March. Aventis's supply is timely. Merck is filling all orders for their Hep B/Hib combination vaccine on time, and they are the only remaining supplier of PPV.

Mr. Mason summarized that the supply of DTaP, Td, MMR and varicella is sufficient for a return to the full dosing schedule. The PCV-7 supply remains sporadic and must continue to be prioritized to high risk children, but the supply could well stabilize and be sufficient to meet national demand consistently in the second quarter of 2003. Some Hib supply delays are expected from Merck at least into March, 2003, but they are delivering Hep B/HIB without delay. NIP believes that Aventis and Merck have the ability to supply HIB vaccine in sufficient amounts to meet national need. This is especially true if Wyeth re-enters the HIB vaccine market in late summer or early fall, 2003.

Discussion with Mr. Mason included:

- *The problem with the meningococcal supply is that it comes in 10-dose vials that must be reconstituted and used within 10 days. Most practices do not see 10 cases in 10 days.* Mr. Phil Hosbach acknowledged that and announced Aventis's return policy of credit for five doses returned. Aventis Pasteur is working with FDA to extend the allowable time after reconstitution to ~1 month, and to get single doses back on line. They hope to have the latter before colleges resume their schedules this fall.
- *The national need is based on the birth cohort, but what about the stockpile?* There is widespread support for pediatric vaccine stockpiles, and $171 has been budgeted for FY03 to expand those. CDC hopes in four years to have a 6-month national stockpile for all routinely used pediatric vaccines. Those are being prioritized for stockpile purchase according to disease threat, transmission mode, production ability, etc. Vaccines that may be added to the stockpile this year are hepatitis A and B and perhaps Hib. The administration is committed to purchase >$700 million in stockpile vaccines in the next four years.
- *Can other countries buy PCV-7 from Wyeth?* Dr. Paradiso said yes, but only in limited quantities, and most other countries recommend it only for high risk groups. Wyeth's goal with CDC now is to make the supply consistent. He was confident that the next couple of months' supply would be adequate and hoped it to be subsequently more secure and consistent. Wyeth is instituting redundancies in the manufacturing process until the supply stabilizes.

VARICELLA VACCINATION PROGRAM UPDATE

Dr. Jane Seward and Dr. Aisha Jumaan presented data on varicella incidence, post-licensure studies of vaccine effectiveness, risk factors for vaccination failure (age at vaccination, time since vaccination, asthma and/or steroid usage; other), transmissibility of vaccinated cases; and addressed the question of whether vaccination will temporarily increase herpes zoster.

Varicella incidence. A *decline in varicella disease* was demonstrated in active and passive surveillance case reports, from active surveillance of hospitalizations, and deaths reported by the National Center for Health Statistics (NCHS). The decline is great among all age groups, but most dramatically among infants and young children. The decline in hospitalizations paralleled the varicella decline in surveillance and that of varicella deaths among children and adolescents aged <20 years – from 53 in 1990 to 8 deaths in 2000.

Vaccine Efficacy. Monitoring of *post-licensure effectiveness of varicella vaccine* showed effectiveness for protection against all disease of 44-100% (from 70-90% pre-licensure) and 75-100% effectiveness in ameliorating moderate to severe disease, versus 95% effectiveness in moderating severe disease pre-licensure. An recent article noted the lower effectiveness and prompted discussion about whether two doses should be provided.

However, Dr. Seward made the point that vaccine effectiveness can be measured in several ways. One is outbreak investigations, which have a bias towards underestimating vaccine effectiveness, since they are based on vaccine failure rather than success. Other methods are case control and prospective cohort studies, and CDC has examined secondary attack rate in household data. She described a few examples.

A varicella outbreak occurred in New Hampshire in a child care center with 92 attendees housed in two separate buildings. The index case was a healthy vaccinated boy exposed to his sister's herpes zoster who developed 150 vesicles and a fever of 102.5_F. The outbreak totaled 25 cases among 17 vaccinated and 8 unvaccinated children. In the building where the index case attended, the secondary attack rate averaged 48.4%, 45.8% in vaccinated children and 57.1% in those not vaccinated.

The overall vaccine effectiveness was 44.0% and 86% to prevent moderate or severe disease. The vaccinated cases experienced much milder symptoms (88% with <50 lesions, less fever, etc). The children vaccinated >3 years before the outbreak had a greater risk of vaccine failure (RR of 2.6) and younger median age at vaccination was associated with vaccine failure (18.4 months at vaccination versus 24.7 months, p= 0.04).

Vaccine effectiveness. Studies of vaccine effectiveness include outbreak investigations, case control and prospective cohorts, and assessment of secondary attack rates in households. The outbreak investigations have a bias toward underestimating vaccine effectiveness since they generally only look at failures, not successes. However, vaccine effectiveness ranged from 71% to 90% in fourteen outbreak investigations done with CDC's help.

The risk factors for vaccine failure include age at exposure, asthma/RAD and/or steroid use, age at vaccination and time since vaccination, and MMR vaccination given within 28 days of varicella vaccination. Asthma was raised as a risk factor since the introduction of varicella

vaccine. CDC examined the VSD data and, after controlling for steroid use, found no effect from asthma alone, prescription for oral steroids within 3 months of vaccination, or inhaled steroids preceding vaccination or disease. But an effect was seem for systemic steroid use (Verstraeten, *Pediatrics*, in press). Studies of vaccine effectiveness according to age at vaccination include four outbreak investigations, Galil's analysis of the New Hampshire outbreak (*NEJM*, 2002) and Verstraeten's retrospective cohort. They showed an effect smaller than those of the outbreak investigation. However, these are all univariate analyses that do not control for time since vaccination.

SKB pre-licensure clinical trial efficacy data on Varilrix vaccine showed less effectiveness in the 10-18 month old age group compared to the 19-24 month (82%) and 25-30 month (77%) age groups (Varis T and Vesikari T, *JID*, 1996). The Galil study and the Berrios study of the Maryland outbreak (*IDSA*, 2002) examined time since vaccination. The variables of age at vaccination and time since vaccination are highly correlated, but those independent effects cannot be studied in outbreak investigations. The risk factor of MMR vaccination given within 28 days and eczema/steroid use will also be mentioned in the *Pediatrics* article..

CDC will next collaborate with Merck and the VSD collaborators with Phase IV data on 90,000 children vaccinated during the pre- and post-licensure studies. That size data set will allow examination of independent effects of all these different risk factors.

A study of *transmissibility of vaccinated (breakthrough) cases* was done using the data from Antelope Valley, CA, active surveillance sites. From 1997-2001, these data included 1349 primary cases, 102 co-primary, 101 secondary and 64 tertiary cases. The vaccine efficacy for all disease was 78.9% and 93.1% for moderate/severe disease. Vaccinated breakthrough cases in a household setting are half as likely to transmit as unvaccinated cases in the same setting.

Three studies of varicella transmission from breakthrough cases in three outbreaks (New Hampshire, Maryland and Maine) were outlined.

- In a child care center outbreak (New Hampshire, 2002), the index case was a healthy 4 year-old vaccinated child who was a high transmitter (~50% SAR), and was suspected of transmitting to his mother, who developed severe illness.
- In a school outbreak (Maryland, 2002) the index case was a healthy 6 year-old vaccinated child. The last 2 cases in outbreak were vaccinated and occurred 13 days apart.
- A school outbreak (Maine, 2003) began with a 7 year-old vaccinated child, whose 39 year-old mother developed rash onset 15 days later. She was hospitalized for three days with severe varicella and dehydration and transmitted the varicella to her 7 month old infant whose rash also emerged 15 days later.

Discussion included:

- *Are there any data to indicate that potentially less potent vaccines were used, as another risk factor?* The state of Massachusetts tracked every reported vaccinated case and looked at storage/handling for each, including records 2-3 years before a challenge. No clustering in outbreaks by provider or lot number was found.

- *Do the data indicate anything about the need for a second vaccination?* There is insufficient evidence to date; more information is needed, including on the risk factors for vaccine failure.

- *What in the Galil study design, method, analysis, etc., can explain the lower vaccine effectiveness?* The children in New Hampshire in winter may have been inside more, leading to a higher transmission rate, or this may have been due to chance.

- Dr. Offit applauded the data's demonstration of clear decreases in disease, hospitalization and deaths, due to the vaccine. He hoped public health would take the time to allow itself some joy at these successes.

- *The issue of vaccination at an early age and waning immunity is important, posing implications to MMR and MMRV vaccine. Are any immunological studies planned?* Some of those data from the clinical trials were to be addressed at this meeting, but there are no immunogenicity data by age. Dr. Barbara Kuter, of Merck, reported that in the 1990s, Merck compared one versus two doses, administered 3 months apart. The titers in the two-dose group were 12-fold higher. And, using as a correlate of protection gp120 ELISA titers >5, they moved the >5 responders to virtually 100%. Over 9-10 years, they followed those children for exposures and disease. The number of cases was small, but there were three times more cases in the one-dose group than the two-dose group. This indicates increased efficacy for two doses, as found with MMR vaccine. Those data will be published soon.

- Dr. Birkhead commented, though, that having lived through a 2-dose measles recommendation that damaged credibility, he would be reluctant to issue a second dose recommend until all the data are in.

Risk Factors for Herpes Zoster

Dr. Jumaan presented the risk factors for herpes zoster, which increase with age. About 20% of the general U.S. population has zoster. The annual incidence is 600,000-850,000, and 50% of the cohort survives to age 85. Zoster risk factors include white race, cell mediated immunity dysfunction, psychological stress, and physical trauma.

There is some thought, related to the childhood varicella vaccination program, that exposure to the varicella zoster virus (VZV) virus may boost immune response, preventing or postponing development of herpes zoster (Hope-Simpson, 1965).

Edmund et al (*Vaccine*, 2001) published a study of the annual burden of zoster and varicella in England and Wales, demonstrating a much lower burden of cost to society from the latter. However, those with zoster may be older, with other contributors to health care costs. A CDC study of hospitalizations in Connecticut from 1986-1995 found 17% of varicella patients with an underlying conditions versus 31% of those with zoster. Incidence rates indicate that those vaccinated have lower risk of zoster infection.

Two previous studies (Japanese and American) provided evidence of an external boosting factor, including that: pediatricians and general practitioners have lower zoster incidence; vaccinated leukemic children with household exposure to varicella were significantly less likely

to develop zoster; an apparent boost from exposure to VZV-specific cellular immunity; that inactivated vaccine for bone marrow transplant patients reduced the risk of zoster; and that immunization appears to boost VZV specific T-cells and may protect against zoster.

In more recent studies, Thomas, Wheeler and Hall *(Lancet* 2002) explored both social and occupational contact with children. They found social interaction with children to be protective but not significantly so (OR 0.8, 0.9), and exposure to household children was not protective. There was no explanation for that. But exposure to more than three children with varicella was protective against zoster. There was some evidence of a dose response in that those with three exposures had only 20% of the risk of zoster compared to those unexposed.

A prospective survey (Brisson et al, *Vaccine* 2002) of morbidity in general practice also showed that living in households with children produced lower rates of herpes zoster. Living with at least one child <15 years was protective against zoster (p value < 0.001) and a Poisson regression modeled the incidence ratio at 0.74 independent of age. Young adults living with children also had a higher varicella incidence rate than those who do not, inferring that exposure to VZV is likely to be greater in all adults living with children.

A chart of the Thomas data showed a lower incidence of zoster in the ≥50 year-old age group which would be expected to have higher rates. The question was whether that result was the influence of person hours of exposure to children, or simply that older people are not around children?

Dr. Seward's published data (*JAMA*, 2002) on the decline of varicella incidence was also modeled to predict the impact of varicella vaccination on herpes zoster. Another figure demonstrated the potential danger of an increase in zoster due to the reduction in varicella cases due to vaccination. The base case model predicts that zoster cases will increase for the first 20 years after the start of varicella vaccination, peaking at an incidence 39% higher than the pre-vaccination level. The incidence of zoster would then gradually decrease as the vaccinated cohorts begin to reach the age at which most zoster occurs. However, the incidence is expected to remain above the pre-vaccination level until 30 to 44 years after the introduction of vaccination. The question is whether society would make the choice in this case, as is made for retirement, of investing 30-40 years in advance. ~~is done in other areas (e.g., retirement);~~.

So, the predictions were that there will be short- and medium-term increases in zoster, mostly among those who had varicella (those who were vaccinated have a lower risk) for ~46 years post-vaccination. The increase would be primarily among those >5 years, 50% of that being in those aged 10-44 years old. But there will be a long-term sustained decline in zoster. The question then is whether the age of zoster would be shifted to a younger age with milder effects, therefore contributing to long-term immunity.

The study's limitations include that it is an ecological study that assumes equivalent exposures to varicella among the children and does not control other risk factors. Less healthy persons are more likely to have zoster and may be less likely to have children in the house, as are those aged >50.

A number of questions were raised by these analyses. For one, if external boosting is the sole determinant of protection against herpes zoster, then how much of the increase in zoster is speculative, how much exposure is needed to benefit, and for how long does the boosting persist? Would there be a difference in effect according to health status (i.e., healthy versus immunocompromised)? Since maintaining immunity to VZV is complex, involving both external and internal boosting, data will have to be monitored to determine any trend. Using inactivated vaccine among bone marrow transplant patients has been shown to reduce the risk of zoster, and the results of adult trials to prevent herpes zoster will be important.

U.S. herpes zoster surveillance was summarized as reported in the Massachusetts BRFSS survey and an ongoing study by the Group Health Cooperative (GHC) in Seattle, WA. The Massachusetts survey 1998-2000 showed a steep decline in varicella, and a decline in herpes zoster from 1999-2000. However, the numbers were small.

The GHC examined medical encounter and telephone consultation records to assess varicella and herpes zoster incidence since 1992. The GHC data reflected a steep decline in varicella incidence by age and year, from 1400 per 100,000 in 1992 to ~20/100,000 in 2000. But this was not paralleled in zoster; which in fact increased in the past few years, reflecting a doubling of the older population.

CDC's current and future plans are to monitor the trends in herpes zoster (understanding pre-vaccine epidemiology, interpreting variations in year to year incidence) and following the adult trial for prevention/modification of zoster. A positive outcome will have great public health significance for persons with history of varicella. Current zoster research continues with the GHC and Massachusetts' BRFSS to examine the incidence of varicella and zoster, and to investigate zoster cases in individuals aged <20 years. Retrospective and ongoing zoster data will be collected.

Future plans included study of the risk factors for herpes zoster using a case control study, examination of the independent effects of vaccination and the incidence of varicella and zoster in multiple areas with southern California Kaiser, and examination of the incidence of zoster in areas of 90% vaccination coverage.

In discussion, Dr. Levin appreciated hearing the data from England, which provides a different perspective. He noted, however, that the BRFSS depends on personal recall, versus the medical record data provided by the GHC.

Data Relevant to VZV Vaccine Efficacy Issues

Dr. Philip R. Krause, of the FDA/CBER, reported on Merck's 15-year follow-up on varicella vaccine. He shared the data of the first 8-year serologic follow-up after vaccine introduction. Most children were immunized in 1992-93 at ages ranging from 1-11 years. Over time, the overall varicella antibody titers increased, as shown by gpELISA antibody assay. The greatest increases occurred in the early years, perhaps because with age these individuals are less likely to be exposed to other children with varicella, and so may no longer be boosting these antibody types. Some of the early titer increase may also be due to asymptomatic reactivation of the vaccine strain, or it may be that the decline of wild-type boosting may be causing a decline in immunity among those immunized.

Long term follow-up: In general, the severity of disease experienced by the vaccinees remained constant over time (mild). They also tracked the cohort's breakthrough rates and found improved protection against severe disease. A telephone interview is done by Merck every five years to determine the annual varicella incidence in these cohorts, by age. That data from 1995 (none vaccinated) to 2000 showed breakthrough varicella rates declining from those of their earlier years. Children with lower titers (<1.25) developed less severe disease, but those with higher titers had much lower incidence.

Merck's serological gpELISA titer assays showed a limited protection at ≥0.6 . Up to 30% of children have some protection from maternal antibody at 12 months, but that declines to the background of the population by 15 months. The GMT over time was analyzed by age and initial serostatus at immunization. Thirteen-month old seropositives had a GMT of ~1.0 and paralleled the levels of seronegatives over time. Compared to levels of older children (c. 18 months), low levels of maternal antibody do not appear to interfere with vaccine take. Breakthrough rates were also followed in the first two years after vaccination. The 12-13 month-old seropositive children had slightly higher breakthrough rates in years 1 and 2, but both groups had lower breakthrough rates than the 14-18 month-old seronegatives. However, the numbers were small.

In summary, the post-licensure studies showed VZV titers rising over time, although they stagnated in the last few years. Breakthrough rates tend to decrease as children get older and less heavily exposed. The severity of varicella does not increase with time from vaccination. There was no observed shift of disease burden to older adolescence. Regarding the potential effect of maternal antibody, 30% of 12 month-olds had some maternal antibody, but it was low and they still responded to vaccination. Antibody titers of those children with maternal antibodies are similar over time to those of older children and seronegatives as vaccination. There is no evidence for increased breakthrough rates, although the data are limited.

Regarding the issue of a second dose of varicella vaccine, Dr. Krause thought that giving it or not depends on the real or perceived impact of breakthrough disease on public health and on individuals, and on the ability of the second dose to prevent further disease. But the present situation, in terms of breakthrough rates, is not comparable to those of measles when the second dose of MMR was clearly necessary (from 1990–91, there were 50,000 cases, 11,000 hospitalizations and 23 deaths).

Discussion with Dr. Krause included:

- *Can you explain the epidemiologic observation that breakthroughs are related to young age at vaccination and the antibody results reported?* The groups were vaccinated at different times than those in Dr. Seward's recent outbreak data, and this vaccine was given under well controlled study conditions. There may be some differences in the field. Some studies have not shown that difference in outbreaks. But understanding who is at risk also has a big impact on the second dose decision. If it is those 12-15 month-old children, the second dose would not be given. By the time dose two was due, they would be of an age in which that would not be a problem. But if the problem is waning immunity, dose 2 could be helpful in reducing the impact of breakthrough varicella.

- We do not yet know if the issue is waning immunity or vaccine failure. Dr. Cooper's study of measles and the importance of exposure to boost vaccination followed two groups, one of institutionalized children and another of those in a health plan. With exposure there was a rapid transient rise in antibody, but it dropped off quickly to the pre-exposure level. The question was whether this relates to antibody level or cellular immunity.

- Dr. Florian Schudel, of Wyeth Research Laboratories, commented that the Krause data showed a striking difference in how measles behaves compared to varicella. The latter's titers increase over time after vaccination, and the booster amplifies that another 10-20 fold, something not seen in measles. Dr. Birkhead wondered if this also could be attributed to the difference in naturally occurring disease at the time of the varicella boost in the last few years, versus the case with measles in the 1980s, which was at historically low levels.

- This all happened in the context of environmental boosting and there has not been time to see what happens naturally. But older people getting zoster have maintained good antibody levels against VZV.

- *Is there a sense that in later years, there are more children at very low levels, who might be the breakthrough cases of the future?* The raw data might answer that, but this study also did not have enough children to explore such a question.

- *Perhaps the timing could be changed for immunizing the 12-18 month-old children, rather than making a programmatic decision to involve a second dose. But the study data differs from outbreak investigations; are there any other data to inform this?* Dr. Seward responded that the phase IV data of the 90,000-strong cohort will hopefully provide the answer in next 12 months.

- Dr. Trudeau commented, regarding boosting, that the responses to the measles vaccine's second dose boost are not accomplished as readily as are varicella's. It is very different from the three other viruses in these combinations. He also reported that they will have second dose data published soon on a longitudinal cohort followed in 3-month intervals.

- Dr. Myers noted that the timing of the measles immunization relative to that for varicella differs between the differing data sets. The issue of difference in breakthrough rates to the timing and the relationship of measles to the varicella vaccine perhaps should be examined more closely.

CHANGING EPIDEMIOLOGY OF PNEUMOCOCCAL DISEASE

Dr. Cindy Whitney, of NCID, outlined ACIP's recommendations on polysaccharide pneumococcal conjugate vaccine (PCV7). PCV7 was licensed in November 2000 and then recommended by ACIP for all children aged <2 years, and for those aged 2-4 years with certain chronic illnesses and immunocompromising conditions. Its use can be considered for all children age 2-4 with priority to those aged 24-35 months, those who are Alaskan Native, American Indian, or African American, and those attending day care. The vaccine's uptake was so rapid that it has been in short supply since August 2000. In view of that, vaccination of healthy children has not been a priority.

Prelicensure studies have demonstrated the vaccine's efficacy in preventing invasive disease caused by the vaccine serotypes, otitis media, and pneumonia. They also indicated potential benefit in preventing disease caused by vaccine-related serotypes, reducing transmission of pneumococci to produce herd immunity. Replacement disease caused by non-vaccine types is possible.

CDC has been tracking invasive pneumococcal disease through the Active Bacterial Core (ABC) surveillance system in seven states. A case is identified when pneumococcus is isolated from a normally sterile site. Surveillance personnel actively contact clinical laboratories to identify cases and then conduct audits to ensure complete reporting. Chart review is done for clinical information and serotyping and susceptibility testing is done at reference laboratories

A chart showed the dramatic results of the vaccine on invasive pneumococcal disease. From 1998-2001, it fell from 70% baseline rates for disease caused by the vaccine serotypes among children aged <1 year, and 44% for those aged <2 years, for vaccine-related strains. There was a slight but not significant increase in non-vaccine strains. For invasive disease rates by vaccine serotypes, a 78% reduction was seen for children aged <2 and for vaccine serotype and 50% for vaccine-related serotypes, alongside a 27% increase in the non-vaccine group.

Studies have shown that adults living with young children have higher carriage rates. The pneumococcal conjugate vaccine was hoped to change that cycle of transmission from children to adults, and the ABC data indicated that this has happened. A herd effect was seen in an 18% decrease in those aged >65, a small but significant change (-8%) in those aged 40-64, and a good 32% drop in those aged 20-39. There was no change in those aged 5-19 years.

Studies of invasive disease in those aged ≥65 also showed changes in vaccine serotype and vaccine-related serotype (-29% and -22%, respectively), alongside a 5% increase in non-vaccine type disease. Reductions in those aged 20-49 were 40% and 22%, respectively, for vaccine serotype and vaccine-related serotype. There was also a 20% reduction for non-vaccine strains, marginally significant but interesting.

The ABCs' data on changes in rates of invasive disease caused by isolates intermediate or resistant to penicillin showed a decrease in rates from 1999 to 2001. Among those aged <2 years, the drop was 70% and 67% among penicillin non-susceptible and penicillin susceptible disease, respectively, and 35% and 27% for all ages. The Healthy People 2010 goal (14-5) to reduce all invasive disease in children aged <5 years to 46/100,000 has been met, with the rate now at 39.7. The goal of 42/100,000 adults aged ≥65 years is close to being met, at 49.7, a considerable drop from the baseline rate of 60.1.

Great progress has been made, but there is still a way to go to reach the goal of reducing penicillin-resistant invasive disease in children aged <5 to 6/100,000; the rate is now 12.7; and for adults 65+ years (goal of 7/100,000), the rate is 12.6.

The conclusions are that conjugate vaccine is working well in young children, in spite of the shortage that caused missed doses, that a herd immunity effect in adults is substantial and conferring fewer deaths and hospitalizations, and that reductions in disease caused by resistant

strains is promising. The remaining questions include 1) how far will the disease drop; 2) will replacement disease occur; and 3) what is the effect on non-invasive disease (i.e., pneumonia)?

Dr. Whitney asked the ACIP, given that this success occurred even with the shortages, if the regular schedule should be changed to three doses rather than four.

Discussion with Dr. Whitney included:

- *What is the role of Pneumovax in the elderly?* That has different serotypes than those in Prevnar; the rates in those types did not change from 1998-2001.

- *England just inaugurated a booster for HiB due to concern that disease was not controlled sufficiently with just primary immunization.* Agreed, that would have to be considered.

- ACIP 2-3 years ago considered reducing doses for IPV and HiB and found that it is very difficult to do. This is a very similar situation.

- *Does this effect correlate more to where vaccine shortage was less of a problem?* There are differences in the magnitude of the change between the surveillance areas. CDC tried to get vaccine coverage data to match up to that, but do not have the data to show that.

- *Are there data on what proportion of children did not receive 4 doses?* CDC heard that some proportion did receive four doses in the shortage while others went unvaccinated. That needs to be examined in the next year.

- *This is kind of an ecologic study. What effectiveness studies of vaccinated and unvaccinated cohorts are there?* CDC is doing a large case-control study of post-licensure effectiveness that is ongoing; some results should be ready in the fall.

- Dr. Paradiso reported Wyeth's interest in the percentage of children who received booster doses. Based on the utilization rates, the marketing staff estimated that 20-25% of children received four doses.

Considerations for Resuming the Routine Pneumococcal Schedule

Dr. Whitney summarized the ACIP's shortage recommendations to give the full series to all children with high-risk medical conditions but not to vaccinate healthy children ≥24 months; to withhold a fourth dose from healthy children aged <24 months; and to ration other doses based on the local supply. No third infant dose should be given if the shortage is severe.

The questions to address to determine when the shortage is over include, using CDC's data on doses delivered: 1) when the average number exceeds the established national need for four months and no orders remain unfilled; or 2) the manufacturers project adequate deliveries. The question then is, which children need catch-up doses? The vaccine supply may be inadequate for catch-up of all partially vaccinated children. The monthly vaccine requirement for the regular schedule is 1.3 million doses and catch-up of partially vaccinated children may require 3.8 - 7.6 million doses.

The priorities suggested were to assign the top priority to high-risk children aged 2-59 months with an incomplete series; followed by unvaccinated healthy children aged 12-23 months; and finally healthy children aged <12 months with <3 doses.

In considering which children may need special visits for catch-up vaccination, it was considered that many children can receive the vaccine at their regular well-child visits in their first 2 years. But special notification may be necessary for children in priority groups who have completed their 15-month visit and have no scheduled visit before age 2, and who receive vaccines at clinics that are not sites of regular health care (e.g., health department).

Dr. Whitney asked if the ACIP wished to make a recommendation to this effect, to review a draft and endorse the statement with a vote at the June meeting? The questions put to the committee were: 1) when should the shortage be declared over?; 2) which children need catch-up doses?; 3) which children need special visits for catch-up vaccination?; and 4) should the ACIP endorse this statement with a vote at the next meeting?

Discussion included:

- The way the ACIP has dealt with shortages in the past has been active involvement in rearranging the schedule to handle it, but also being very loose about letting the program decide when the shortage was over. The pneumococcal vaccine situation is not different. The NIP is appropriately monitoring the situation, but ACIP will help as best it can.

- The ACIP could review the status at the June meeting, and NIP could have discussions with the workgroup in the interim. However, the Pneumococcal Conjugate Workgroup has not been active since the ACIP statement was published.

- Dr. Orenstein reported that the questions posed to ACIP were discussed somewhat at the Red Book meeting. He wished to discuss them at the June meeting, based on the vaccine supply available. Dr. Baker expected no problem if there is a good continuous supply. At most, which children may need special visits for catch-up vaccination may need to be addressed. But if a good supply does not continue, the Red Book Committee will have to go back to giving guidance about which doses to skip, the associated logistics, etc. The ACIP should wait until June to know if and when the shortage is over.

- Dr. Wharton suggested that an ACIP member join the ad hoc workgroup formed with the AAP. Dr. Brooks volunteered.

- Dr. Whitney will send out a draft recommendation prior to the June meeting.

CLOSING COMMENTS

Workgroups. Dr. Modlin asked if there were enough data to warrant forming an ACIP workgroup to address adolescent and adult pertussis. Dr. Wharton hoped for guidance from such a group. CDC could assemble the specific information requested by the workgroup for the ACIP's address of this vaccine.

The current ACIP workgroups address: 1) PCV-7, 2) adolescent/adult pertussis vaccine, 3) the joint workgroup with NVAC on the polio vaccine stockpile (2-3 ACIP members); and 4) the

small workgroup on evidence-based tables and the evidence basis for making recommendations. Dr. Modlin asked if there were enough data on the herpes simplex vaccine to warrant a workgroup. Dr. Tompkins reported that the workgroup had not worked on this since CDC's attention has been devoted to the smallpox activity. She suggested merging the HSV and HPV groups. She expressed her own preference to work on the Pertussis Workgroup, but her term has expired. Dr. Modlin liked the idea of merging the two groups and pointed out that workgroups go beyond individuals' tenures.

Dr. Snider reassured the committee that CDC is close to agreement with the DHHS on replacements for those members who were to rotate off last year and for Dr. Natalie Smith's seat. The other package of nominations has to be assembled and resubmitted by the end of March. The speed of the Department's response is unpredictable, but if not by June, CDC would at least want the present members to return for the October meeting.

Dr. Modlin asked members interested in any of these workgroups to advise him or the ACIP office of that, so that they could be assembled by the next meeting. He agreed to remind the members of this request. He reminded them as well that these workgroup can include non-ACIP members, although the Chair is generally an ACIP member. Dr. Snider hoped that the members would continue to participate after their membership ends, since this is important to the workgroups' continuity.

With no further comment, the meeting adjourned at 2:35 p.m.

I hereby certify that to the best of my knowledge, these minutes are accurate and complete.

John Modlin, MD, Chair

Date

ATTACHMENTS

Attachment #1: Attendance

Chair: John F. Modlin, MD
Executive Secretary: Dixie Snider, MD, MPH

ACIP Members

Guthrie S. Birkhead, MD, MPH
Dennis A. Brooks, MD, MPH
I. Celine Hanson, M.D.
Myron J. Levin, MD
Paul R. Offit, MD
Margaret B. Rennels, MD
John Salamone
Lucy S. Tompkins, MD, PhD
Bonnie M. Word, MD
Richard Zimmerman, MD

Members absent were: Jaime DeSeda, M.D. and Celine I. Hanson, MD. Robert B. Belshe, MD, had resigned from the committee.

Ex-Officio Members

Centers for Disease Control and Prevention
Alison Mawle, MD, National Center for Infectious Diseases (NCID)
Walter Orenstein, MD, National Immunization Program (NIP)
Dixie Snyder, MD (ACIP Executive Secretary)
Charles Vitek, MD, National Center for HIV, STD, and TB Prevention (NCHSTP)
Melinda Wharton, MD, NIP

Other Federal Agencies
Benjamin Diniega, Department of Defense (DOD)
Geoffrey Evans, National Vaccine Injury Compensation Program (NVICP)
Bruce Gellin, Director Designate, National Vaccine Program Office (NVPO)
Randolph Graydon, Center for Medicare and Medicaid Services (CMS)
Carole Heilman, National Institute for Allergy and Infectious Diseases (NIAID)
Karen Midthun Food and Drug Administration (FDA)
Kristin Nichol, Department of Veterans' Affairs (DVA)

Liaison Representatives
Carol Baker and Julia McMillan, American Academy of Pediatrics (AAP)
Stanley Gall, MD, American College of Obstetricians and gynecologists (ACOG)
Geno Germano, Pharmaceutical Research and Manufacturers of America
Randolph Jackson, National Medical Association (NMA)
Samuel Katz, Infectious Disease Society of America (IDSA)
Martin Mahoney, MD, PhD, American Academy of Family Physicians (AAFP)
Victor Marchessault, National Advisory Committee on Immunization, Ontario, Canada
David Neumann, National Coalition for Adult Immunization (NCAI)
Kathleen Neuzil, American College of Physicians (ACP)
Georges Peter, National Vaccine Advisory Committee (NVAC)
Robert Scalettar, Md, MPH, American Association of Health Plans (AAHP)

William Schaffner, Infectious Disease Society of America (IDSA) and Guide for Adult Immunization
Jane Siegel, Hospital Infections Control and Prevention Advisory Committee (HICPAC)
Litjen Tan, Ph.D., American Medical Association (AMA)
James Turner, MD, American College Health Association (ACHA)

Agency Staff

Centers for Disease Control and Prevention (CDC)
Unidentified C/I/O: Eleanor McClellan, Kathryn Monto, Monica Panse, Pauline Terebuh, Eddie Wilder
Michele Bailey, CDC Hotline, North Carolina

Epidemiology Program Office (EPO): Rosaline Dhara, Tom Torok

National Center for Birth Defects and Developmental Disorders (NCBDDD): Joe Mulinare

National Center for Infectious Diseases (NCID)

Craig Borkowf	Nancy Cox	Steve Ostroff
William Bower	Roz Dewart	Sean Polock
Caroline Bridges	Anthony Fiore	Lisa Rotz
Lynette Brammer	Scott Harper	Theresa Turski
Martin Cetron	Barbara Herwaldt	Tim Uyeki
Shadi Chamany	Rema Khabbaz	Cynthia Whitney
Soju Chang	Alison Mawle	Jennifer Wright
Myrna D.Charles	Ann Moen	
Joanne Cono	Ida Onorato	

National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP): Sheryl Lyss

National Center for HIV, STD, and TB Prevention: Marta Ackers, Brad Barthalow, James Heffelfinger, Scott Santibanez

National Immunization Program (NIP):

Curtis Allen	Gary Coil	Pauline Harvey
Carolyn Bachino	Margaret Cortese	Beth Hibbs
Brooks Barry	Gustavo Dayan	Sonya Hutchins
Achal Bhatt	Christine Robinette Curtis	Marika Iwane
Kris Bisgard	Rex Ellington	Alan Jansson
Karen Broder	Christine Ernst	Laurie A. Johnson
Kristin Brusuelas	Gary Euler	Deva Joseph
Scott Campbell	Katie Fullerton	Sharon Katz
Christine Casey	Edith Gary	Maureen Kolasa
Bob Chen	Jayne Gaskins	Brock Lamont
Pamela Ching	Penina Haber	Larry LaRue
Susan Chu	Jim Harrison	Charles LeBaron

Joan C. Lipton
Sherry D. Lome
Peng-Jun Lu
Adam MacNeil
Mehran Massoudi
Elaine Miller
Mona Marin
Dean Mason
Mike Menril
John Moran
Arnaldo Muralles
Trudy Murphy
Glen Nowak
Diane Z-Ochoa
Carolyn O'Mara
Dennis O'Mara
Ismael Ortega-Sanchez
Larry Pickering
Vitali Pool
Jean Popiak
Susan Reef
Lance Rodewald
Marty Roper
Tammy A. Santibanez
Jean Santoli
Ben Schwartz
Jane Seward
Kristine Sheedy
Judith Shindman
Jim Singleton
Natalie Smith
Vishnu Priya-Sneller
Pamela Srivastava
Tejpratap Tiwari
Fran Walker
Eric Weintraub
Skip Wolfe
John X. Zhang
Laura Zimmerman

National Vaccine Program Office (NVPO): Steve Sepe

Office of General Counsel: Kevin Malone

Department of Defense (DOD): John D. Grabenstein

Members of the public or presenters to the committee in attendance were:
Bryan Bechtel, Infectious Diseases in Children, Thorofare, NJ
Don Beeman, Merck & Co., Inc.
Joan Benson, Merck
Ron Bittone, Merck Vaccine Division
A. Monica Bologa, Aventis Pasteur
John Boslego, Merck
Andrew Bowser, freelance medical writer, Brooklyn, NY
Kim Bush, Baxter Pharmaceuticals
Dan Casto, Merck
Ivan Chan, Merck
Lisa Clowers, HDMA
Kathleen Coelingh, MedImmune Vaccines
Kevin Colley, Maxim Health Systems, Winter Park, FL
Michelle Conner, GA Immunization Program
Dack Dalrymple, Dalrymple & Associates/Pink Sheet, Washington, D.C.
Michael Decker, Aventis Pasteur/Vanderbilt University
Richard C. Dinovitz, Wyeth
Greg Dotson, GSK
Stephen Douthwaite, GSK
Steven Foster, American Pharmaceutical Association
Betsy Frazer, AQAF, Vestavia Hills, AL
Joan Fusco, Baxter Pharmaceuticals
Diana Gaskins, GA Immunization Program, Atlanta, GA
Genn Germano, Wyeth
Ruth Gilmore, GA Immunization Program, Atlanta, GA
Eric Greenbaum, Merck

Jesse Greene, South Carolina Department of Health and Environmental Control
Dave Gutsch, Merck
Neal Halsey, Johns Hopkins University, Baltimore, MD
Daniel Halstrom, GSK
Claire Hannan, Association of State and Territorial Health Officers (ASTHO)
Scott Harvard, GSK
Adnan Hatimi, GSK
Rick Haupt, Merck & Co., Inc.
Sandra Holmes, GSK
Philip Hosbach, Aventis Pasteur
Barbara Howe, GSK
Robbin Itzler, Merck Research Laboratories
Melonie Jackson-Kronmeyer, Georgia Chapter, AAP
Richard Judelsohn, MD, Erie County Department of Health, Buffalo, NY
Barb Kuter, Merck
Dr. J. Michael Lane, ORISE, Oak Ridge, TN
Jo LeCouilliard, GSK
Marie-Michele Leger, AAPA
Josephine Li-McLeod, Baxter
Harold W. Lupton, Aventis Pasteur
Anita Manning, USA Today, Wilmington, DL
Michele Marill, Hospital Employee Health
Michele Mattide, Aventis Pasteur
Maryn McKenna, Atlanta Journal Constitution, Atlanta, GA
Martin Myers, UTMB, Galveston, TX
Karen Nielsen, GSK
Peter Paradiso, Wyeth Vaccine, West Henrietta, NY
Stanley Plotkin, MD, Aventis Pasteur, Doylestown, PA
Vladimir Popovic, VaxGen
James Ransom, National Association of City and County Health Officers (NACCHO)
A. Rogers, Parallax, Indianapolis, IN
Heather Rose, Cohn-Wolfe, NY
Fred Rubin, Aventis Pasteur
Brent Rutland, Aventis Pasteur
Bill Salas, GSK
David Sammons, GSK
Michele Schimmel, Cohn & Wolfe
Jody Schollenberger, Merck Vaccine Business
Florian Schudel, Merck
Amy Scott-Billman, GSK
Kirit Shah, Aventis Pasteur
Josephine Seiberlick, GSK
Dr. Alan J. Sievert, East Metro Health District, Lawrenceville, GA
J.L. Silber, Merck
Barbara A. Slade, MD, Serologicals, Inc., Decatur, GA
Ben Sloat, GA Division of Public Health
Parker Smith, IMN

Dan Soland, GSK
Judy Stewart, GSK
Jefferey Stoddard, MedImmune
Kathleen Stratton, Institute of Medicine (IOM)
Dr. Kathleen Stratton, IOM
Stacy Stuerke, Merck Vaccine Division
Eric Tischler, Aventis Pasteur
Karen Townsend, GA Chapter, AAP
John Trezzino, Henry Schein, Inc.
James C. Turner, MD, American College Health Association
Minaxi Upadhyaya, Association of State and Territorial Health Officials (ASTHO)
Tom Vernon, MD, Merck Vaccine Division, West Point, PA
Peter Vigliarolo, Cooney Waters, New York, NY
Nancy Walsh, Pediatric News
Martin Wasserman, GSK
Deborah Wexler, Immunization Action Coalition, St. Paul, MN
Matthew Williams, Flu Central, Doraville, GA
Steve Wright, Maxim Healthcare
Dan Ye, Associated Press
Greg Yoder, Merck & Co.
Laura York, Wyeth Vaccines
John Zahradnik, Aventis Pasteur
Thomas Zink, GSK Vaccine, Philadelphia, PA

Attachment #2: Tables of VaxGen Vaccine Efficacy Trial Results

Vaccine Efficacy			
Weighted Cohort			
	Placebo Inf./total	**Vaccine Inf./total**	**VE (95.12%CI)**
All Volunteers	3.8% (-22.9 - 24.7%)	98/1679 (5.8%)	191/3330 (5.7%)
White & Hispanic	81/1508 (5.4%)	179/3003 (6.0%)	-9.7% (-42.8 to 15.7%)
Black/Asian/Other	17/171(9.9%)	12/327 (3.7%)	66.8% (30.2 to 84.2%)*
Black	9/111 (8.1%)	4/203 (2.0%)	78.3%(29.0 to 93.3%)**
Asian	2/20 (10.0%)	2/53 (3.8%)	68.0% (-129.4 to 95.5%)
Other	6/40 (15.0%)	6/71 (8.5%)	46.2% (-67.8 to 82.8%)

* $p < 0.01$
** $p < 0.02$

Vaccine Efficacy: Weighted Cohort			
MEN			
	Placebo Inf./total	**Vaccine Inf./total**	**VE (95.12%CI)**
All Volunteers	94/1586 (5.9%)	190/3155 (5.7%)	0.7%(-27.3 to 22.6%)
Black/Asian/Other	13/116 (11.2%)	12/231 (5.2%)	59.5% (10.9 to 81.6%)
White & Hispanic	81/1470 (5.5%)	178/2924 (6.1%)	-8.8% (-41.7 to 16.4%)
WOMEN			
All Volunteers	4/93(4.3%)	1/175 (0.6%)	86.4% (-22.8 to 98.5%)
Black/Asian/Other	4/55 (7.3%)	0/96 (0%)	—
White & Hispanic	0/38	1/79 (1.3%)	—